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Sustained released Metformin microparticles for better management of type II diabetes mellitus: *in-vitro* studies

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Keywords: metformin, ethylcellulose, microparticles, sustained release, encapsulation efficiency

Abstract

This work investigates Ethyl cellulose (EC) and polyethylene glycol (PEG) microparticles for prolonged delivery of Metformin HCl. The microparticles were synthesised by emulsion solvent evaporation technique; characterized for encapsulation efficiency, particle size, flow properties, surface morphology, FTIR, PXRD and drug release pattern; and investigated for the effect of formulation parameters like EC:PEG ratio, drug to polymers ratio and stirring speed on various properties of the microparticles. The drug entrapment efficiency, percent yield, particle size and drug release behaviour were found to be influenced by various formulation parameters. SEM images and size analysis confirmed formation of spherical shaped microparticles, with slightly rough surface and good flowability. FTIR revealed absence of any drug-polymer interaction and PXRD confirmed the molecular dispersion of drug with in microparticles. All the formulations showed sustained drug release pattern at pH 6.8, up to 91.34% $\pm$ 1.68 metformin was released in 12 h with fickian diffusion mechanism. The designed microparticles could possibly be advantageous in terms of prolonged release, to achieve reduced dose frequency and improved patient compliance.

1. Introduction

Metformin HCl, a biguanide is widely used hypoglycemic agent for the management Type II diabetes mellitus either alone or in combination with other anti-diabetic drugs [1, 2]. It is also reported to be beneficial for dyslipidemia, elevated

plasma-plasminogen activator inhibitor, fibrinolytic abnormalities, insulin resistance and may stop the growth of tumor cells [3]. The drug is primarily absorbed from the small intestine, having a short biological half-life of 1.5–1.6 h and the daily requirement of 1.5–3 g/day [4].

Therefore, the marketed immediate release product needs to be administered 2–3 times daily to maintain effective plasma concentration [5]. These drawbacks can be overcome by designing suitable sustained release metformin HCl formulations, reducing the dosing frequency and improving the patient adherence to prescription.

Among various oral sustained drug delivery systems, polymeric microparticles are one of the options. These have been studied in past few decades for targeted delivery with specificity, better oral bioavailability, reduced side effects and less dosing frequency [6, 7]. In general, polymeric microspheres consist of polymeric matrix, in which active pharmaceutical agents are dispersed, entrapped, or adsorbed that can release entrapped drug through diffusion [8], providing uniform distribution of drug throughout the GIT, allowing uniform drug absorption hence decreased patient to patient variation after oral drug administration [9, 10]. A number of different polymers both biodegradable and non-biodegradable have been investigated for preparation of polymeric microparticles. Among these EC, a water insoluble, hydrophobic, non-biodegradable, biocompatible, high pressure resistant and non-toxic cellulose polymer, is extensively used for the formulation of pharmaceuticals [11]. This polymer is often used as a rate-controlling membrane to modulate the drug release from dosage forms with organic or aqueous coating techniques [12–14]. Polyethylene glycol (PEG), also known

Table 1. Formulation parameters of prepared Metformin HCl-loaded microparticles.

Formulation code	Polymer to drug ratio	EC:PEG	Metformin HCl (g)	Polymer (g)	
				Ethyl cellulose	PEG
EP-1	2:1	1:1	0.5	0.5	0.5
EP-2	2:1	1.5:1	0.5	0.6	0.4
EP-3	2:1	2:1	0.5	0.67	0.33
EP-4	2:1	4:1	0.5	0.8	0.2
EP-5	4:1	1:1	0.5	1	1
EP-6	4:1	1.5:1	0.5	1.2	0.8
EP-7	4:1	2:1	0.5	1.4	0.7
EP-8	4:1	4:1	0.5	1.6	0.4
EP-9	6:1	1:1	0.5	1.5	1.5
EP-10	6:1	1.5:1	0.5	1.8	1.2
EP-11	6:1	2:1	0.5	2.1	0.9
EP-12	6:1	4:1	0.5	2.4	0.6

as polyoxyethylene and polyethylene oxide is nontoxic and rapidly cleared from body. It is soluble in water, benzene, dichloromethane and insoluble in hexane and diethyl ether. PEG has been used in combination with other polymers as drug release modifier [15, 16].

In present study, a series of EC/PEG microparticles with varying polymers ratio, drug to polymer ratio and stirring speed were prepared for sustained delivery of Metformin HCl and the effects of above mentioned variables on the drug entrapment efficiency, particle size and in-vitro drug release behaviour were investigated.

2. Materials and methods

Metformin was a kind gift from Hamaz Pharmaceuticals Multan. Ethylcellulose (N-10) and Polyethylene glycol were purchased from Merck (Germany). Tween 80 was obtained from England Labs Chemicals) and Dichloromethane was sourced from BDH.

2.1. Preparation of ethylcellulose and polyethylene glycol microspheres of metformin

Microspheres were prepared by emulsification solvent evaporation method [17]. Accurately weighed quantities of ethyl cellulose (EC) and polyethylene glycol (PEG) (Table 1) were dissolved in 20 ml of dichloromethane (DCM) by hot plate stirring for 30 min at 500 rpm, while metformin (500 mg) was dissolved in 10 ml of distilled water. After mixing drug and polymer solution at 800 rpm for 1 hr, the solution was added drop wise by using syringe, at room temperature under constant stirring at 800 rpm, to 100 ml of 0.5% (w/v) tween 80 aqueous solution. Stirring was continued over 60 min until complete evaporation of DCM. After the evaporation of DCM, the recovered microparticles were washed repeatedly with distilled water in order to remove any adhering particles and to remove the impurities. The microparticles were isolated on a filter paper and dried first at room temperature and then in the oven at 37 °C to assure moisture free microparticles. Unloaded (drug-free) microparticles were

prepared using same experimental conditions but in the absence of metformin HCl.

2.2. Estimation of percentage yield

Percentage yield was calculated with the help of following equation (1):

$$\text{percent yield} = \frac{\text{total amount of recovered microparticles}}{\text{amount of drug} + \text{amount of polymer}} \times 100 \quad (1)$$

2.3. Estimation of drug loading and drug entrapment efficiency

Accurately weighed microparticles were dissolved in dichloromethane and then diluted with phosphate buffer. The solution was kept on stirring for 1 hr for the complete evaporation of DCM and polymer was separated by filtration. The amount of drug was determined by using UV-Visible spectrophotometer at 232 nm. The percent drug loading was calculated as (equation (2)):

$$\text{Drug loading (\%)} = \frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres}} \times 100 \quad (2)$$

The drug entrapment efficiency (%) of these microspheres was calculated by the following formula (equation (3)):

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug load}}{\text{Theoretical drug load}} \times 100 \quad (3)$$

2.4. Rheological studies

All prepared formulations were subjected to rheological studies to determine angle of repose, tapped density, bulk density, Carr's compressibility index and Hausner ratio [18].

Angle of repose of different formulation was calculated according to fixed funnel standing method using equation (4).

$$\tan \theta = \frac{h}{r} \quad (4)$$

Where, θ is angle of repose, r is radius and h is height.

Bulk and tapped densities were measured using 10 ml of graduated cylinder. The bulk density of a material is the ratio of the mass to the volume (including the interparticulate void volume) of an untapped powder sample (equation (5)).

$$\text{bulk density} = \frac{\text{mass of sample}}{\text{volume of sample}} \quad (5)$$

Tapped density was calculated by measuring tapped volume after tapping the cylinder mechanically for 200 times (equation (6)).

$$\text{tapped density} = \frac{\text{mass of sample}}{\text{volume after tapping}} \times 100 \quad (6)$$

Compressibility Index (Carr's index) was calculated according to following equation (7):

$$\text{carr's index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \quad (7)$$

Hausner's ratio was used to calculate flow ability of the microparticles and was determined by comparing the tapped density to the bulk density using equation (8).

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad (8)$$

2.5. Scanning electron microscopy (SEM)

SEM was used to determine the surface topology of the microparticles and was examined by scanning electron microscope (SEM-Jeol Instruments, JSM-6360, Japan).

2.6. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of metformin, drug-free microparticles and drug loaded microparticles were recorded with Attenuated total reflection fourier-transform infrared (ATR-FTIR) spectrophotometer (Bruker IR Affinity 1 Model, Japan), in the range of 4000 to 400 cm^{-1} .

2.7. Powdered x-ray Diffraction (PXRD)

X-Ray diffraction pattern of pure drug, drug loaded and unloaded microparticles were recorded on powder x-ray diffractometer. X-ray diffractometer (JDX 3532, JEOL, Japan) with Cu radiation at 50 mA and at 60 kV. Samples were irradiated with mono achromatized x-rays and XRD pattern observed through scanning rate of 2° per minute.

2.8. In-vitro drug release studies

In-vitro drug release profile of metformin HCl microspheres was determined by using USP dissolution apparatus II (paddle method) connected with Auto Sampler (Pharma test PTFC 2, Germany). Precisely weighed microparticles were taken in small dialysis bag (dialysis membrane 800 Da) tied with paddle and dipped in dissolution flask. Dissolution studies were performed in 0.05 M phosphate buffer (pH 6.8) for 12 h at 35 ± 0.5 °C under 100 revolutions per minute. Samples of about 3 ml were withdrawn (in triplicate) at various time intervals i.e. 0.25, 0.5, 1, 2, 4, 6, 8, 10 & 12 h from middle of flask for UV analysis. Withdrawn amount were replaced with relevant fresh buffer solutions. All samples were filtered through 0.22 μm membrane and then

Table 2. Effect of drug-polymer ratio and polymers (EC: PEG) ratio on the drug content, percent yield, particle size and size distribution of the Metformin loaded EC/PEG microspheres.

Code	% yield (mean $\pm$ S.D)	Drug loading (%) (mean $\pm$ S.D)	Entrapment efficiency (%) (mean $\pm$ S.D)	Mean particle size (μm $\pm$ SD)	Polydispersity index
EP-1	46.66 $\pm$ 2.42	30.33 $\pm$ 1.21	32.98 $\pm$ 2.53	15.44 $\pm$ 2.341	0.301 $\pm$ 0.04
EP-2	50.66 $\pm$ 1.52	33.26 $\pm$ 2.15	36.76 $\pm$ 1.62	28.00 $\pm$ 0.925	0.327 $\pm$ 0.37
EP-3	57.33 $\pm$ 2.36	38.19 $\pm$ 1.85	39.90 $\pm$ 1.94	45.76 $\pm$ 1.125	0.338 $\pm$ 0.028
EP-4	58.66 $\pm$ 2.04	46.09 $\pm$ 1.01	44.45 $\pm$ 1.75	65.95 $\pm$ 2.36	0.31 $\pm$ 0.041
EP-5	70.4 $\pm$ 0.69	57.89 $\pm$ 2.25	53.38 $\pm$ 1.38	77.03 $\pm$ 1.55	0.368 $\pm$ 0.037
EP-6	71.6 $\pm$ 2.03	62.09 $\pm$ 1.64	57.78 $\pm$ 2.98	89.54 $\pm$ 2.11	0.369 $\pm$ 0.028
EP-7	72.8 $\pm$ 2.09	67.98 $\pm$ 1.95	61.09 $\pm$ 1.63	93.54 $\pm$ 0.89	0.371 $\pm$ 0.036
EP-8	75.2 $\pm$ 2.54	72.05 $\pm$ 0.98	66.56 $\pm$ 1.12	124.01 $\pm$ 2.00	0.399 $\pm$ 0.047
EP-9	75.14 $\pm$ 1.54	79.21 $\pm$ 0.99	71.88 $\pm$ 1.42	136.21 $\pm$ 1.36	0.408 $\pm$ 0.028
EP-10	78.23 $\pm$ 2.99	80.25 $\pm$ 1.11	76.54 $\pm$ 2.43	140.08 $\pm$ 2.27	0.518 $\pm$ 0.015
EP-11	79.71 $\pm$ 1.51	80.08 $\pm$ 1.57	79.09 $\pm$ 2.55	165.08 $\pm$ 0.221	0.537 $\pm$ 0.033
EP-12	81.71 $\pm$ 2.08	82.1 $\pm$ 1.83	82.13 $\pm$ 1.51	178.12 $\pm$ 3.24	0.584 $\pm$ 0.045

analyzed for Metformin using Ultraviolet Visible Spectrophotometer (UV-1601, Shimadzu) at 232 nm after subsequent suitable dilution.

2.9. Release kinetic studies

The drug release kinetics was obtained by fitting the drug release data to zero order, first order, Higuchi model and Hixson Crowell [18, 19].

Korsmeyer and Peppas equation (equation (9)) was applied to interpret the mechanism of drug release from the microparticles.;

$$\frac{M_t}{M_0} = k_3 t^n \quad (9)$$

where, M_0 and M_t are the amount of drug released at time zero and the amount of drug released at time t respectively, k_3 represents rate constant and n is the diffusional exponent.

The values of n were determined from the slopes and intercepts of the straight line. For the spherical matrices, in case of a Fickian (case-I) drug release mechanism n is <0.43 , for anomalous or non-Fickian mechanism n is $0.43 < n < 0.85$ and a case-II (zero order) drug release mechanism n is >0.85 [20].

3. Results

3.1. Percent yield, drug content, average particle size and size distribution

The results for the percent yield, drug content and average particle size of microspheres (EP-1-EP-12) are reported in table 2. A perusal to table 2 indicated that percent yield of microspheres was in the range of 46.66% $\pm$ 2.42 to 81.71 $\pm$ 2.08. The drug entrapment efficiency was within the range of 32.89% $\pm$ 2.53 to 82.13% $\pm$ 1.51 and drug loading was up to 82.1% $\pm$ 1.83. The mean particle size was in the range of 15.44 μm $\pm$ 2.341 to 178.12 μm $\pm$ 3.24 and the polydispersity index was below 0.584.

3.2. Morphological and Rheological evaluation

The SEM photographs (figure 1), revealed that the metformin microparticles were spherical in shape.

All preparations were studied for the rheological properties and results are presented in table 3. Angle of repose for microspheres was between 20.21° to 31.33°, Carr's index (Ci) was less 20 for all formulations and Hausner's ratio was in the range of 1.09–1.23.

3.3. In-vitro dissolution and drug release kinetics

In vitro drug release pattern of metformin HCl loaded EC/PEG microparticles was observed at pH 6.8 by using phosphate buffer. All the formulations showed sustained release pattern (figure 2). In first three hours of dissolution studies burst release of metformin HCl was observed followed by slow release over next 9 h of the study. After 12 h of dissolution studies maximum drug release (91.3% $\pm$ 1.68) was observed in formulation with lowest polymer to drug ratio of 2:1 (EP1), while minimum drug release (72.87% $\pm$ 1.86) was observed with highest polymer to drug ratio of 6:1 (EP12). In set of formulations EP1-EP4, EP5-EP8 and EP9-EP12; with increasing content of EC in comparison to PEG and constant polymer drug ratio, cumulative percent release was

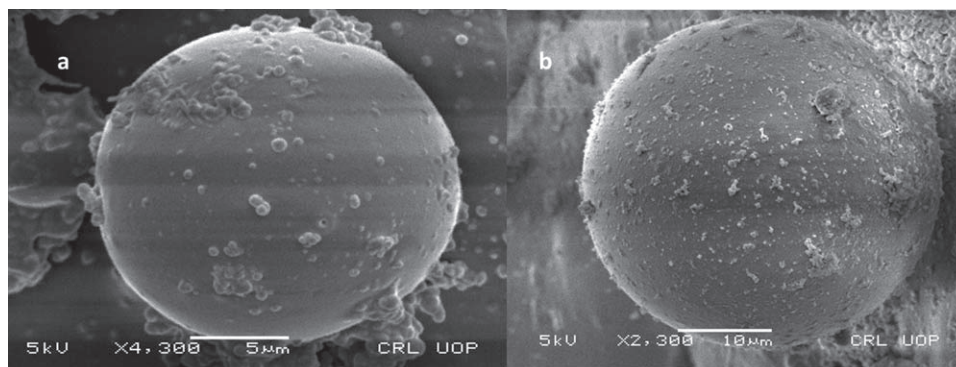


Figure 1. SEM photograph of drug loaded microparticles (a) at 1000 rpm (b) at 800 rpm.

Table 3. Rheological evaluation of microparticles.

Code	Angle of repose ($\theta \pm \text{SD}$)	Bulk density ($\text{g}/\text{cm}^3 \pm \text{SD}$)	Tapped density ($\text{g}/\text{cm}^3 \pm \text{SD}$)	Carr's index ($\% \pm \text{SD}$)	Hausner's ratio ($\% \pm \text{SD}$)
EP-1	20.21 ± 1.68	0.27 ± 2.05	0.32 ± 1.68	18.75 ± 2.13	1.23 ± 1.43
EP-2	21.21 ± 1.12	0.28 ± 2.65	0.33 ± 2.68	18.18 ± 2.35	1.22 ± 2.69
EP-3	24.21 ± 1.43	0.28 ± 1.38	0.34 ± 3.12	17.64 ± 2.42	1.21 ± 1.74
EP-4	23.21 ± 1.05	0.29 ± 2.16	0.35 ± 3.54	17.14 ± 1.33	1.20 ± 1.08
EP-5	27.21 ± 2.65	0.3 ± 2.13	0.35 ± 3.85	14.28 ± 2.65	1.16 ± 1.247
EP-6	28.21 ± 2.65	0.32 ± 1.77	0.36 ± 2.43	11.11 ± 1.37	1.12 ± 1.93
EP-7	29.21 ± 1.08	0.35 ± 2.06	0.39 ± 2.85	10.25 ± 1.85	1.11 ± 1.08
EP-8	31.33 ± 1.33	0.34 ± 2.05	0.38 ± 1.48	10.52 ± 2.65	1.11 ± 1.47
EP-9	30.54 ± 1.47	0.39 ± 2.26	0.43 ± 1.07	9.3 ± 2.33	1.10 ± 2.05
EP-10	27.21 ± 2.26	0.40 ± 1.35	0.45 ± 2.35	11.11 ± 3.01	1.12 ± 1.38
EP-11	24.21 ± 1.18	0.42 ± 0.65	0.46 ± 1.22	8.69 ± 0.65	1.09 ± 2.33
EP-12	25.22 ± 1.34	0.43 ± 2.25	0.47 ± 1.08	8.5 ± 3.24	1.09 ± 1.20

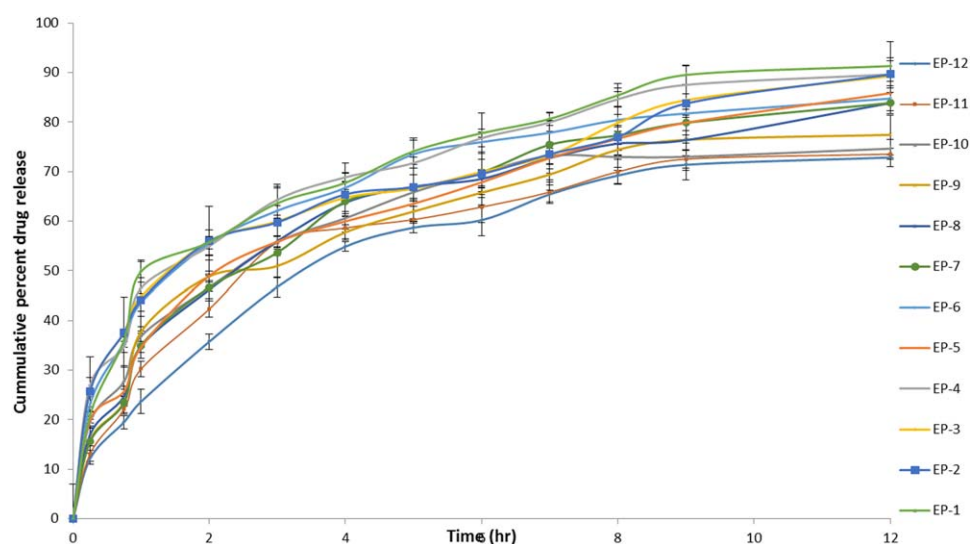


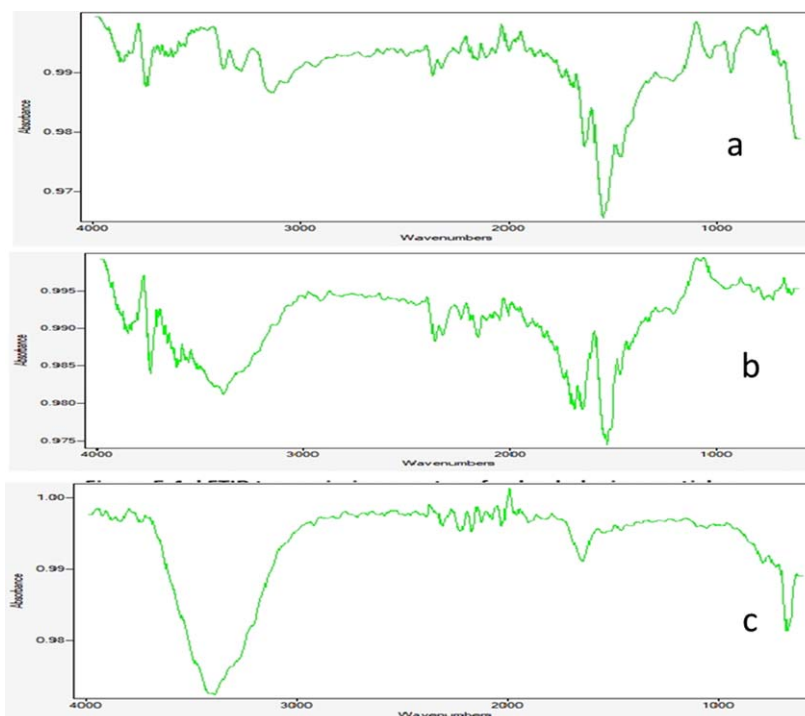
Figure 2. *In vitro* Metformin release profile at pH 6.8.

decreased from $91.34\% \pm 1.6$ to $89.65\% \pm 2.6$; $85.87\% \pm 2.4$ to $83.87\% \pm 2.1$ and $77.45\% \pm 4.01$ to $72.87\% \pm 1.86$ respectively.

The data was fitted to several kinetic models and best fit model was selected on the basis of regression coefficient (r). Results of model fitting, as presented in table 4, showed that the formulations followed Higuchi model (0.963–0.987), with Fickian diffusion release mechanism.

Table 4. Results of regression coefficients of the model fitting of metformin release data from microparticles.

Formulation	Zero order		First order		Higuchi model		Hixson-crowell		Korsmeyer-peppas	
	k_0	r	k_1	R	k_H	R	k_{HC}	r	k_{kp}	n
EP-1	8.783	0.87	0.186	0.963	25.271	0.969	0.050	0.947	32.467	0.364
EP-2	8.514	0.91	0.166	0.984	24.189	0.986	0.046	0.972	27.281	0.435
EP-3	9.22	0.86	0.216	0.966	26.733	0.964	0.057	0.948	36.916	0.324
EP-4	9.182	0.88	0.203	0.970	26.394	0.97	0.054	0.956	34.197	0.359
EP-5	9.60	0.89	0.226	0.981	27.56	0.980	0.060	0.968	34.860	0.373
EP-6	9.757	0.90	0.231	0.985	27.912	0.982	0.062	0.975	34.174	0.390
EP-7	10.25	0.85	0.296	0.972	29.808	0.963	0.078	0.959	43.002	0.300
EP-8	9.68	0.91	0.225	0.980	27.720	0.987	0.060	0.970	35.019	0.373
EP-9	10.65	0.87	0.322	0.974	30.859	0.971	0.083	0.963	43.947	0.307
EP-10	10.16	0.88	0.273	0.958	29.412	0.971	0.070	0.945	42.561	0.298
EP-11	10.11	0.88	0.270	0.957	29.262	0.971	0.069	0.943	42.465	0.296
EP-12	10.80	0.87	0.333	0.974	31.253	0.970	0.083	0.968	43.556	0.319

**Figure 3.** FTIR spectra of (a) Metformin, (b) drug loaded microparticles EP-4 and (c) empty microparticles.

3.4. FTIR Spectroscopy:

FTIR spectra of metformin HCl (figure 3(a)) illustrated peaks at 3169 cm^{-1} , 1063 cm^{-1} and 1584 cm^{-1} representing N-H stretching, C-N stretching and N-H bending respectively. FTIR spectra of empty microspheres (figure 3(c)) depicted characteristics peaks at 3480 cm^{-1} representing OH stretching, at 2974 cm^{-1} representing CH_2 stretching, at 1102 cm^{-1} for C-O-C stretching and at 949 cm^{-1} characterizing C-H bending. The identical peaks of N-H stretching, C-N stretching, and N-H bending vibrations were also appeared in the spectra of metformin loaded PEG/EC microspheres (figure 3b).

3.5. Powder x-ray diffraction

The sharp intense representative peaks of pure metformin (figure 4(a)) were notably observed at 17.65° , 22.35° , 23.3° , 24.55° , 26.4° , 27.2° , 28.2° , 31.3° , 34.35° , 35.45° , 37.2° and 39.4° ; indicating crystalline state of pure metformin. PXRD pattern of loaded microparticles and unloaded microparticles showed intense peaks at about 21.8° and 23.4° (figures 4(b) and (c)). Peaks corresponding to Metformin were absent in drug loaded microparticles, suggesting dispersion of drug in microparticles at molecular level.

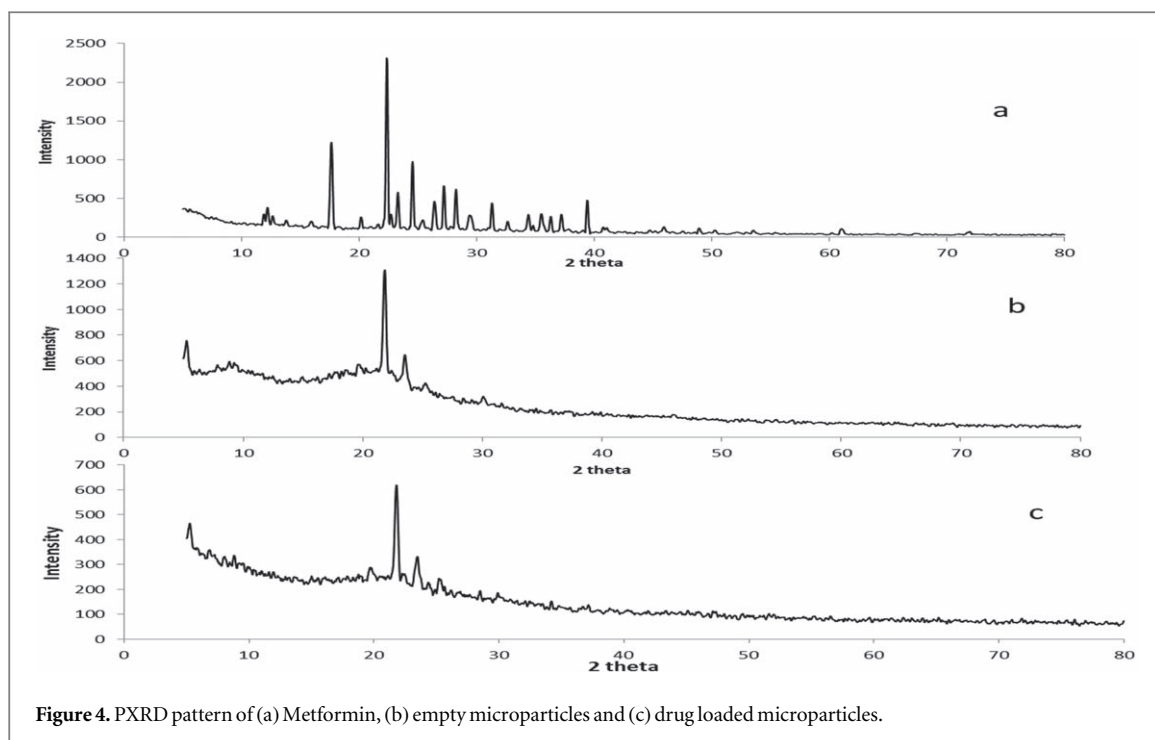


Figure 4. PXRD pattern of (a) Metformin, (b) empty microparticles and (c) drug loaded microparticles.

4. Discussion

In present work, emulsification solvent evaporation technique was successfully utilized for the fabrication of EC/PEG loaded metformin HCl microparticles. In initial trials different stirring speeds (500 rpm, 800 rpm and 1000 rpm) were applied to observe the effect of speed on morphology and percent recovery of the product, and to optimize the reaction conditions. It was observed that the stirring speed below 800 rpm resulted in aggregation and adherence of microparticles to the walls of the beaker, whereas stirring speed above 800 rpm resulted in less percent recovery (data not presented) and de-shaped microspheres (figure 1(a)), while stirring speed of 800 rpm yield uniformly dispersed spherical microparticles (figure 1(b)). Therefore, an optimum stirring speed of 800 rpm was fixed with outcomes of relatively uniform percent recovery and uniform shaped microspheres. Moreover, drug loaded microspheres had rough surfaces might be due to surface adhered drug particles, which are probably responsible for initial burst release of drug during dissolution [21].

From the results of percent yield (table 2), it was observed that with increasing EC polymer content production yield was increased. Moreover, higher drug content (table 2) was observed with decreasing drug-polymer ratio (increasing polymer content); while stirring speed, polymers ratio and surfactant concentration were constant. The higher the polymer content would probably result in large amount of polymer surrounding the drug, which would act as barrier and might not allow the drug to diffuse out from the microspheres into the external phase [17, 22]. A considerable amount of drug up to 82% loaded into the microspheres, a quite common phenomenon with the solvent evaporation method. With increasing polymer: drug ratio from 2:1 to 6:1, comparatively

larger microspheres with relatively higher PDI value were obtained, requiring more energy to break the drug-polymer droplet into smaller particles [23]. These results suggest that formulation variables have considerable effect on drug content, particle size, PDI and recovery of product, thus by varying these parameters formulation with desired features could easily be tailored.

The results of FTIR spectroscopy confirmed OH stretching of PEG, C-O-C stretching, -CH₂ stretching in PEG/EC microspheres [24, 25]. The N-H stretching of primary amine group of metformin, bands for C-N stretching and N-H bending were present in spectra of metformin and metformin loaded microspheres [26]. The presence of all the characteristic peaks of drug in the drug loaded microspheres confirmed the compatibility of drug with the polymers.

Crystal morphology of drug is an important parameter influencing the dissolution behaviour of the drug. The results of PXRD confirmed the crystalline nature of the pure drug, which was molecularly dispersed (amorphous state) into polymer matrix by formulation of the microparticles. This molecularly dispersed drug and small particle size would enhance the dissolution, thus bioavailability of the drug [27, 28]. Rheological studies confirmed the free flowing nature of the microspheres (table 3).

In vitro drug release pattern of metformin HCl loaded EC/PEG showed sustained release behaviour (figure 2). The initial burst release was might be due to surface adhered drug molecules and would serve to reach the minimum effective concentration for pharmacological response. The polymer matrix encapsulating the drug has greatly influenced the % cumulative drug release. It was found to be decreased with increase in drug to polymer ratio, this effect might be attributed to increase in the thickness of matrix resulting in slow drug diffusion to the dissolution medium [29]. As the proportion of EC was increased (EP1-EP4, EP5-EP-8 and EP9-EP12) with constant polymer to drug ratio, the release of metformin was decreased attributed to retarding nature of the EC. Moreover, the higher metformin release in formulations with higher amount of PEG in comparison to EC was might be due water soluble nature of PEG which has enhanced the matrix permeability for the drug, therefore more amount of drug came out of the matrix. These change in pattern of drug release with changing polymer to drug ratio and EC to PEG ratio suggest that by adjusting these variables formulations with desired metformin controlled release pattern can easily be tailored. Various kinetic models were applied to estimate drug release order and in accordance to r values all the formulations followed Higuchi model suggesting diffusion process for drug release. The n value varied from 0.296 to 0.3, indicating Fickian diffusion release mechanism for all formulations.

5. Conclusion

The study concludes that the emulsification-solvent evaporation is a simple and reproducible technique for the fabrication of metformin HCl-loaded ethyl cellulose and polyethylene glycol microparticles. The drug entrapment efficiency, particle size, and drug release behaviour of these microparticles were influenced by drug to polymer ratio and EC to PEG ratios, thus by controlling these formulation parameters microparticles with desired release pattern and size can be prepared. At pH 6.8 sustained release behaviour was observed indicating EC/PEG microparticles as promising metformin carrier for the management of noninsulin-dependent diabetes mellitus. However, authors suggest that selected formulation might be subjected to *in vivo* evaluation in order to further establish the effectiveness, potential benefit and clinical application.

Acknowledgments

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