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Research Article

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS USING POLYELECTROLYTE COMPLEXES

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ABSTRACT

The present study involves formulation and evaluation of sustained release tablets of metformin hydrochloride which is BCS Class-III drug, using polyelectrolyte complexes of gum karaya-chitosan. Formulations were prepared by direct compression method and the optimized formulations were prepared as tri layered tablets using HPMC K100M and PECs for desired release. All formulations were evaluated for various precompression parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The drug and excipients compatibility study was performed by Fourier Transformer Infrared Spectroscopy analysis, Powder X-Ray diffraction analysis and Differential scanning calorimetry. The compressed tablets were evaluated for physicochemical parameters like weight variation, thickness, hardness, friability, drug content and *in vitro* dissolution studies. Results indicated that the pre formulation parameters were within the limits and there was compatibility between the drug and excipients. Results show that as the concentration of PECs was increased the drug release from the matrix tablet was decreased. Initial release from the matrix tablet was 67%. To reduce the release, tri layered tablets were prepared using HPMC K100M and PECs. Initial release was controlled to 25-26%. MH14 and MH16 were considered as optimized formulations and the drug release at 12th h is 97.26% and 96.27% respectively. The regression coefficient values and the "n" values for optimized formulations were 0.986 and 0.983 indicating zero order release and 0.517 and 0.529 indicating an anomalous transport mechanism. The optimized formulation subjected to stability was found to be stable for one month as per ICH guidelines for climate zone III.

Keywords: Polyelectrolyte complexes, tri layered tablets, Fourier Transformer Infrared Spectroscopy analysis, Powder X-Ray diffraction analysis, Differential scanning Calorimetry.

INTRODUCTION

Oral drug release is the most desirable and preferred route of administration for the drug activity into the systemic circulation. Medication through oral route is considered as the first avenue for investigation in the formulation and development of new drugs because of patient compliance, convenience of administration and economic manufacturing process[1]. Though they are advantageous, draw backs are poor patient compliance, increased chances of missing the dose of a drug with short half-life where frequent administration is necessary. Inevitable fluctuations of drug concentration may lead to under medication or over medication. Precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) and the typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.

Oral drug delivery systems can be classified into immediate-release (IR), controlled-release (CR) and Targeted-release preparations. The technologies for CR are diffusion controlled either in matrix or reservoir systems in which drug diffusion is the rate-limiting step. Solvent activated systems, where these may be either controlled by osmotically or swelling of polymer. Chemically controlled systems, in which the release of drugs may be via polymeric degradation (surface or bulk erosion) or cleavage from a polymer chain[2].

Sustained release tablets and capsules are commonly taken once or twice in a day, compared with conventional tablets which are taken three or four times daily to achieve the same therapeutic response. In these types of dosage forms, a sufficient amount of drug is made available to the body initially to cause required pharmacological effect and the remaining fraction is released periodically to maintain the activity for desirable period of time from usual single dose[3].

Continuously growing interest is there in the pharmaceutical industry for sustained release oral drug delivery systems which allows high drug loading. These systems are optimized for Biopharmaceutic, Pharmacokinetic and Pharmacodynamic properties of a drug in such a way that its utility is maximized by reduction of side effects. The cure or control of condition can be achieved in the shortest possible time by using smallest quantity of drug which was administered by the most suitable route. There is also a high interest for design a dosage formulation with high water solubility[4].

MATERIALS AND METHODS

Materials

Metformin Hydrochloride, Chitosan and HPMC K100M are purchased from Yarrow chem Products, Gum karaya, Nutriroma, Magnesium stearate, Hydrochloric acid, Potassium dihydrogen ortho phosphate and Sodium hydroxide pellets are purchased Finar chemicals limited.

Pre formulation Studies

It is primitive step in the rational development of dosage forms. Pre formulation testing is the analysis of physical and chemical properties of a pure drug as well as combination with excipients. Required quantity of each ingredient was taken and subjected to grinding to get the required degree of fineness then passed through sieve no 60. The powder blend was subjected to precompression parameters as discussed further[5].

Flow Properties

Angle of repose

It is the maximum angle formed between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured. The tangent of angle of repose is equal to the co-efficient friction (μ) between the particles. Hence the rougher and more irregular the surface of particles the greater will be angle of repose.

Procedure

100 gm of the blend was accurately weighed and poured through the funnel whose tip was fixed at 2.5 cm height above the graph paper placed on a horizontal surface. The blend was poured till the apex of the pile touches the tip of the funnel. Angle of repose is calculated by the following formula.

$$\theta = \tan^{-1}(h/r) \quad \text{(Eq.3.1)}$$

Where, θ = angle of repose, r = radius of the pile, h = height of the pile

Bulk density

Bulk density is defined as mass divided by the bulk volume of powder.

Procedure

Apparent bulk density (*b) was determined by taking the blend in a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$*b = M/V* \quad \text{(Eq.3.2)}$$

Tapped density

Known mass of blend in a measuring cylinder was tapped (approx 250) for a fixed time. The weight (M) and volume (V_t) occupied in the cylinder was measured. The tapped density (*t) was calculated using the formula:

$$*t = M/V_t \quad \text{(Eq.3.3)}$$

Compressibility index

The measurement of free flow of powder is compressibility and which is calculated using the formula.

$$\text{C.I}\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{(Eq. 3.4)}$$

Hausner's ratio

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the using the formula.

$$\text{Hausner ratio} = *t/*d \quad \text{(Eq.3.5)}$$

Where *t = tapped density.*d = bulk density

Preparation of PECs of gum karaya and chitosan

1.875 g karaya was taken and added to 187.5 ml distilled water in a 250 ml beaker and kept for stirring at 200 rpm on a magnetic stirrer. To this 125 mg chitosan in 12.5 ml of 2% v/v acetic acid in water was added slowly under stirring. Stirring was continued for 10 min. After 1 h of incubation period, the mixture was centrifuged for 10 min at 2000 rpm to separate the precipitated PEC. The supernatant liquid was decanted and the wet mass was dried at 60°C. The dried mass obtained was calculated as given in (Table 1 and Figure 1) then crushed and shifted through sieve no. 60[6-9].

pH and conductivity study

The change in the pH and conductivity with respect to the addition of poly ions at various mixture weight ratios was determined by using pH meter and conductivity meter respectively. 1% w/v stock solutions of karaya gum and chitosan were prepared for the study.

Effect of temperature

The effect of temperature on the formation of PECs was determined at 40 and 60°C.

Preparation of tablets by direct compression

In direct compression method drug and polymer were mixed thoroughly in geometrical proportions and then the remaining ingredients were added and compressed at maximum compression force with 12 mm punch. For formulations (Table 2 and 3)

Evaluation of Sustained Release Matrix Tablets

The prepared tablets are evaluated for various parameters like weight variation, thickness, hardness, friability, drug content, content uniformity and *in vitro* dissolution studies[5].

Weight variation

Twenty tablets were randomly selected, and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness

The thickness of tablet is measured by screw gauge. It is related to the tablet hardness and can be used as an initial control parameter. The thickness in millimeters (mm) was measured individually for five pre weighed tablets by using screw gauge. It should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). From each formulation batch five tablets were tested randomly.

Friability

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber which is set to revolve around 25 rpm for 4 min. For each revolution it drops the tablets at a distance of 6 inches. Pre weighed sample of 20 tablets were placed in the friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula:

$$F\ \% = (1 - W_0 / W) \times 100 \quad \text{.....(Eq.3.6)}$$

Where, W_0 is wt of the tablets before the test and W is the wt of the tablets after test.

Drug content

Twenty tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar and then powder equivalent to 250 mg was weighed and dissolved in 100 ml of 6.8pH buffer, filtered and analyzed by UV spectrophotometer at 233 nm.

Content uniformity

The content uniformity test is used to determine the amount of drug in each of 10 tablets within a batch using the analytical method as mentioned above.

***In vitro* dissolution studies**

The *in vitro* drug release of metformin hydrochloride sustained release tablets was determined using 900 ml of 0.1N HCl for first 2 h, 6.8 pH buffer for next 10 h. Aliquot of 5 ml withdrawn and replaced with 5 ml of the fresh solution with USP Dissolution Apparatus I (basket type) (Electrolab TDT-08L) at 50 rpm. Samples were analyzed by UV spectrophotometer (ELICO- 164 double beam spectrophotometer) at a wavelength of 233 nm.

Drug-Excipient Compatibility Studies

Fourier Transformer Infrared Spectroscopy analysis

The spectrum analysis of pure drug and physical mixture of drug and different excipients were studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 min.

Powder X-Ray diffraction analysis

The crystallinity of the drug, polymer and optimized mixtures were studied by powder XRD. The powder XRD analysis was performed using Shimadzu XRD-7000 X- ray diffractometer using Copper K α (λ = 1.5406 A°) radiation. The data were recorded over a scanning 2θ range of 5^0 to 50^0 at a step time of 0.045 steps/0.5 sec.

Differential scanning calorimetry

DSC analysis was performed using Shimadzu DSC-60 differential scanning calorimeter (DSC) and the instrument was calibrated with indium standard. 3-5 mg samples were weighed and placed in a closed, hermetic sample pans with pin hole. Thermo grams were obtained by heating the sample at a constant rate 10^0C/min in presence of dry purge of nitrogen gas (50 ml/min) for all runs. Samples were heated from 0^0C to 350.0^0C then melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of new peaks and their shapes were noted.

Model Dependent Methods

Regression coefficients (r^2) were calculated for all the formulations. Release component "n" was calculated from Korsemeyer Peppas equation[10-11].

Comparison of Prepared Optimized Formulation with Marketed Formulation

The *in vitro* dissolution release of the optimized formulations was compared with the marketed Glycomet 500 mg SR tablets.

Performing Accelerated Stability Studies for the Optimized Formulations

The optimized formulation was subjected to stability studies at 40^0C ± 2^0C/75% ± 2% RH (zone III) for period of one month. Each tablet was individually wrapped in aluminum foil and packed in amber colored bottle and put at above specified condition in a heating humidity chamber for one month. Tablets were analyzed for the physicochemical evaluation and *in vitro* drug release studies at 1st, 2nd and 4th weeks.

RESULTS AND DISCUSSION

The present investigation was undertaken to formulate and evaluate the sustained release matrix tablets of metformin hydrochloride by polyelectrolyte complexes using gum karaya and chitosan. The main objective of the study was to sustain the drug for 12 h.

Pre formulation Studies

Precompression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. Values for angle of repose were found in the range of 26.47 ± 0.92 to 27.89 ± 0.92 (I.P limits 25-30) showing that the blend of powder was free flowing. The value for carr's index was in between 11.19 ± 0.339 to 14.53 ± 0.926 (I.P limits 11-15) indicating that all batches of powder blends were having good compressibility. Hausner's ratio was to be within the limits 1.126 ± 0.013 to 1.150 ± 0.001 (I.P limits 1.12-1.18). The results showed that all the formulations good blend properties (See Table 4).

Parameters affecting the yield

pH and Conductivity Study

Poly ions posses certain charge when they are present in the aqueous solution. Oppositely charged poly ions form an insoluble polyelectrolyte complex in the aqueous medium. There is a possible change in the charge that may occur when the polyelectrolytes interact and form complexes. These interactions and the formation of PECs can be well studied by pH and conductivity studies[12].

Table 1: Preparation of PECs of gum karaya and chitosan of different ratios

Ratio	Chitosan	Karaya	%Yield
1:5	33.33 mg	166.66 mg	45%
1:10	18.18 mg	181.81 mg	62.5%
1:15	12.5 mg	187.5 mg	91%
1:20	9.52 mg	190.47 mg	71%
1:25	7.69 mg	192.3 mg	60.5%
1:30	6.45 mg	193.54 mg	32%
1:40	4.87 mg	195.12 mg	-

Table 2: Formulations with PECs (Chitosan: Karaya = 1:10 and 1:15)

Ingredients (mg)	Formulations									
	MH1	MH2	MH3	MH4	MH5	MH6	MH7	MH8	MH9	MH10
Metformin hydrochloride	250	250	250	250	250	250	250	250	250	250
Karaya gum	375	113.6	227.27	340.9	117.18	175.78	234.37	292.96	351.56	410.15
Chitosan	-	11.36	22.72	34.09	7.81	11.71	15.62	19.53	23.43	27.34
Magnesium stearate	3	1.8	2.5	3	1.8	2	2.5	2.8	3	3.4
Total weight (mg)	628	356.8	502.5	628	356.8	439.5	502.5	565.3	628	691

Note: MH1-MH4 formulations with PECs (Chitosan: Karaya = 1:10) and MH5-MH10 are with (Chitosan: Karaya = 1:15)

Table 3: Formulations with HPMC K100M and PECs

Ingredients (mg)	Formulations						
	MH11	MH12	MH13	MH14	MH15	MH16	MH17
Metformin hydrochloride	250	250	250	250	250	250	250
Karaya gum	351.56	351.56	351.56	351.56	351.56	351.56	351.56
Chitosan	23.43	23.43	23.43	23.43	23.43	23.43	23.43
HPMC K 100 M	62.5	93.75	125	100	150	-	-
PEC layer	-	-	-	-	-	100	150
Magnesium stearate	3	3	3	3	3	3	3
Total weight (mg)	690	721.74	753	728	778	728	778

Table 4: Pre compression parameters of the powder blend of all formulations

Formulation	Angle of repose (Ɵ)*	Bulk density (gm/cm^3)*	Tapped density (gm/cm^3)*	Hausner's ratio *	Compressibility Index (%) *
MH1	27.26 ± 1.03	0.642 ± 0.014	0.735 ± 0.004	1.144 ± 0.019	12.58 ± 1.520
MH2	27. 12 ± 0.98	0.646 ± 0.006	0.735 ± 0.009	1.137 ± 0.003	12.09 ± 0.233
MH3	26.78 ± 0.82	0.617 ± 0.004	0.722 ± 0.003	1.126 ± 0.013	14.53 ± 0.926
MH4	27.89 ± 0.80	0.634 ± 0.005	0.720 ± 0.008	1.136 ± 0.022	11.99 ± 1.739
MH5	27.21 ± 0.72	0.645 ± 0.005	0.742 ± 0.005	1.150 ± 0.001	13.24 ± 0.169
MH6	26.62 ± 0.53	0.652 ± 0.012	0.740 ± 0.003	1.134 ± 0.021	11.89 ± 0.562
MH7	27.89 ± 0.92	0.669 ± 0.024	0.757 ± 0.002	1.131 ± 0.019	11.62 ± 0.327
MH8	26.47 ± 0.92	0.641 ± 0.004	0.727 ± 0.002	1.134 ± 0.004	11.88 ± 0.332
MH9	26.62 ± 0.90	0.658 ± 0.003	0.749 ± 0.002	1.138 ± 0.002	12.20 ± 0.127
MH10	27.26 ± 1.03	0.642 ± 0.014	0.735 ± 0.004	1.144 ± 0.019	12.58 ± 1.520
MH11	27.12 ± 0.98	0.646 ± 0.006	0.735 ± 0.009	1.137 ± 0.003	12.09 ± 0.233
MH12	27.78 ± 0.82	0.617 ± 0.004	0.722 ± 0.003	1.140 ± 0.013	14.53 ± 0.926
MH13	26.89 ± 0.80	0.634 ± 0.005	0.720 ± 0.008	1.136 ± 0.022	11.99 ± 1.739
MH14	27.21 ± 0.72	0.645 ± 0.005	0.742 ± 0.005	1.150 ± 0.001	13.24 ± 0.169
MH15	27.62 ± 0.53	0.652 ± 0.012	0.740 ± 0.003	1.134 ± 0.021	11.19 ± 0.339
MH16	26.89 ± 0.92	0.669 ± 0.024	0.757 ± 0.002	1.131 ± 0.019	11.62 ± 0.327
MH17	27.62 ± 0.90	0.658 ± 0.003	0.749 ± 0.002	1.138 ± 0.002	12.20 ± 0.127

Values are expressed as Mean ± SD, *n = 3

Table 5: Evaluation of prepared tablets

Formulation	Weight Variation[a] (mg)	Hardness[b] (Kg/cm^2)	Friability[c] (%)	Thickness[d] (mm)	Drug content[e]
MH1	628 ± 0.79	6-7	0.12 ± 0.56	5.82 ± 0.35	97.07 ± 0.01
MH2	358 ± 0.54	3-4	0.23 ± 0.78	4.21 ± 0.41	97.43 ± 0.08
MH3	500 ± 0.36	5-6	0.27 ± 0.23	5.15 ± 0.27	98.71 ± 0.04
MH4	630 ± 0.23	6-7	0.18 ± 0.14	5.82 ± 0.09	98.08 ± 0.22
MH5	357 ± 0.79	3-4	0.21 ± 0.13	4.18 ± 0.58	99.15 ± 0.39
MH6	441 ± 0.36	4-5	0.13 ± 0.67	4.63 ± 0.62	97.54 ± 0.11
MH7	503 ± 0.72	5-6	0.16 ± 0.45	5.15 ± 0.81	98.53 ± 0.05
MH8	566 ± 0.15	5-6	0.21 ± 0.34	5.35 ± 0.04	98.75 ± 0.42
MH9	627 ± 0.37	6-7	0.31 ± 0.56	5.80 ± 0.21	98.67 ± 0.30
MH10	690 ± 0.45	6-7	0.15 ± 0.13	6.14 ± 0.49	97.43 ± 0.05
MH11	628 ± 0.52	6-7	0.12 ± 0.78	6.14 ± 0.31	98.56 ± 0.02
MH12	630 ± 0.71	6-7	0.11 ± 0.59	6.21 ± 0.07	99.18 ± 0.26
MH13	629 ± 0.64	6-7	0.17 ± 0.61	6.36 ± 0.11	98.16 ± 0.81
MH14	728 ± 0.53	6-7	0.15 ± 0.84	6.25 ± 0.69	99.54 ± 0.21
MH15	729 ± 0.72	6-7	0.13 ± 0.91	6.23 ± 0.52	98.63 ± 0.12
MH16	779 ± 0.45	6-7	0.18 ± 0.13	6.45 ± 0.03	98.75 ± 0.23
MH17	778 ± 0.92	6-7	0.15 ± 0.41	6.47 ± 0.14	99.07 ± 0.01
Glycomet 500 mg SR	500 ± 0.41	7-8	0.101 ± 0.26	6.25 ± 0.22	99.11 ± 0.04

Values are expressed as Mean ± SD for a: n = 20, b and d: n = 5, c, e and f: n = 10

Table 6: Model dependent kinetic study for all formulation dissolution profiles

Formulations	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	n
MH1	0.951	0.860	0.987	0.992	0.343
MH2	0.907	0.994	0.978	0.974	0.274
MH3	0.999	0.993	0.995	0.990	0.313
MH4	0.945	0.904	0.977	0.979	0.463
MH5	0.971	0.981	0.991	0.996	0.285
MH6	0.996	0.966	0.999	0.997	0.306
MH7	0.988	0.794	0.992	0.992	0.351
MH8	0.937	0.950	0.984	0.991	0.362
MH9	0.941	0.937	0.988	0.993	0.399
MH10	0.965	0.843	0.993	0.994	0.433
MH11	0.959	0.754	0.983	0.989	0.400
MH12	0.947	0.799	0.983	0.988	0.393
MH13	0.948	0.888	0.988	0.992	0.438
MH14	**0.986**	**0.814**	**0.991**	**0.995**	**0.517**
MH15	0.990	0.809	0.989	0.993	0.512
MH16	**0.983**	**0.872**	**0.990**	**0.994**	**0.529**
MH17	0.990	0.858	0.989	0.993	0.526

Table 7: Physicochemical properties ofMH14 during accelerated stability studies

Parameters	Time in weeks			
	0 (Initial)	1st week	2nd week	4th week
Appearance	White to off white	White to off white	White to off white	White to off white
Hardness (kg/cm^2)	6.5 ± 0.22	6.3 ± 0.13	6.2 ± 0.71	6.1 ± 0.15
Drug content (%)	99.54 ± 0.21	98.16 ± 0.41	97.27 ± 0.68	96.18 ± 0.45

Values are expressed as Mean ± SD, n = 3

Table 8: Physicochemical properties of MH16 during accelerated stability studies

Parameters	Time in weeks			
	0 (Initial)	1st week	2nd week	4th week
Appearance	Light brown	Light brown	Light brown	Light brown
Hardness (kg/cm^2)	6.6 ± 0.12	6.4 ± 0.54	6.2 ± 0.63	6.1 ± 0.89
Drug content (%)	98.63 ± 0.12	97.12 ± 0.45	96.91 ± 0.23	96.82 ± 0.13

Values are expressed as Mean ± SD, n = 3

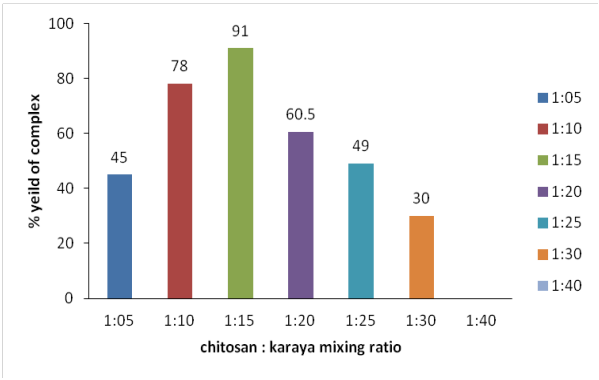


Figure 1: Effect of gum karaya and chitosan mixing ratio on the yield of polyelectrolyte complex

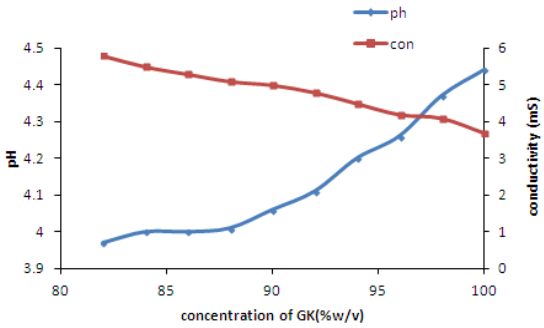


Figure 2: Conductivity and pH profiles during the interaction between GK and CH aqueous solutions

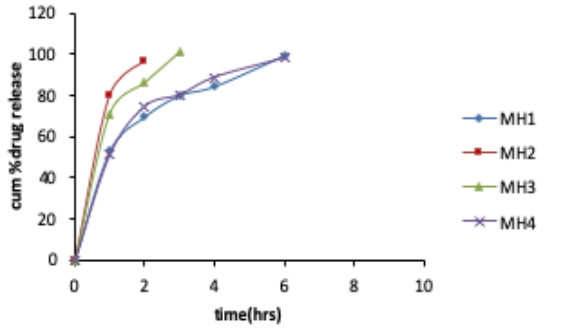


Figure 3: Dissolution profiles of formulations with (Chitosan: Karaya = 1:10)

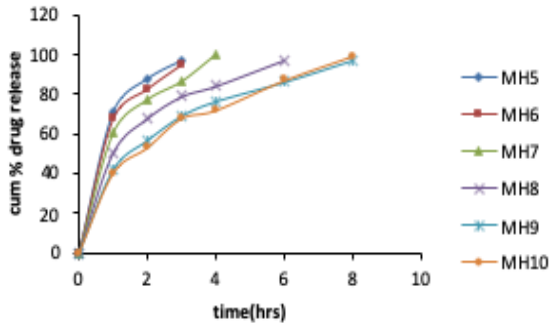


Figure 4: Dissolution profiles of formulations with PECs (Chitosan: Karaya = 1:15)

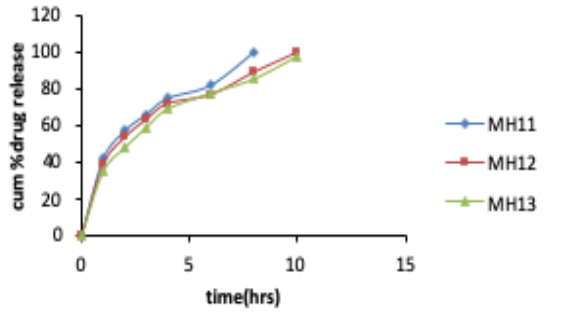


Figure 5: Dissolution profiles of formulations with HPMC K100M

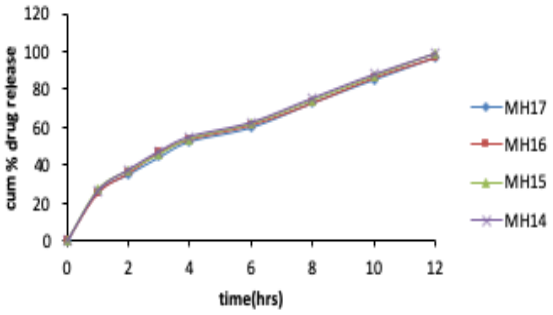
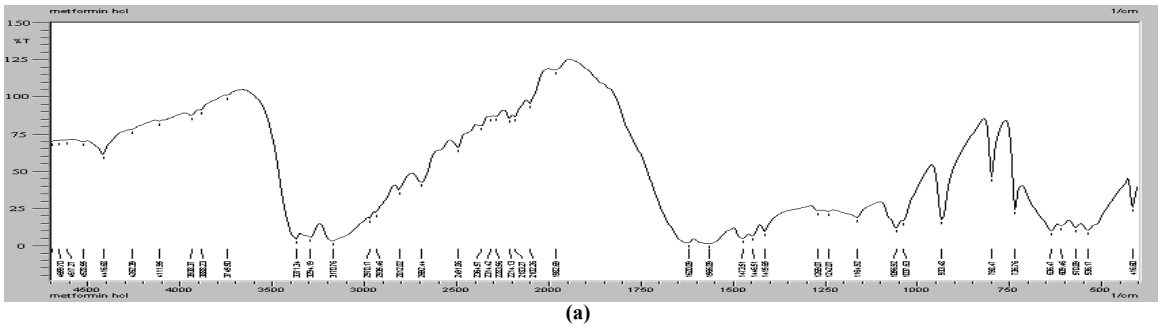
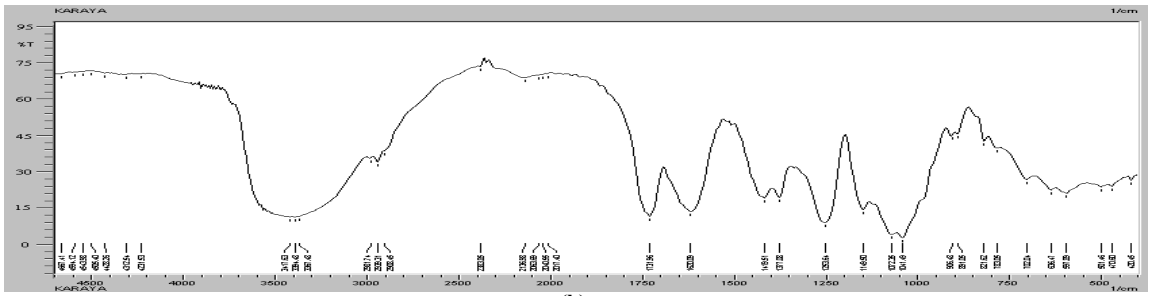


Figure 6: Dissolution profiles of formulations layered with HPMC K100M and PECs

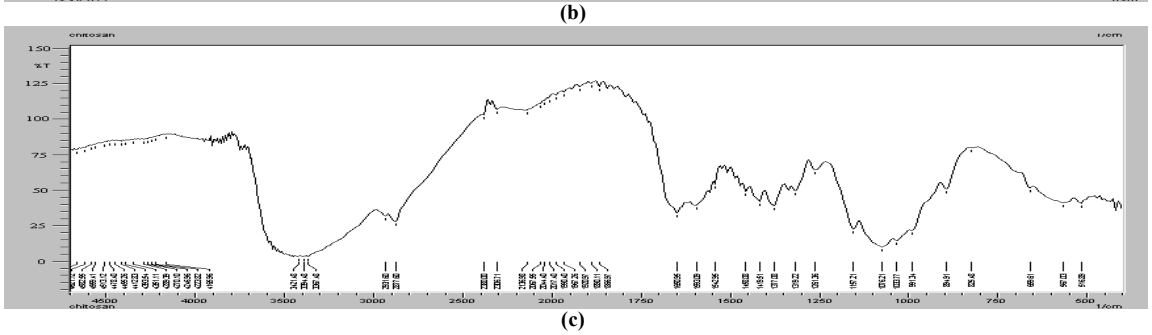
Transformer Infrared Spectroscopy analysis



(a)



(b)



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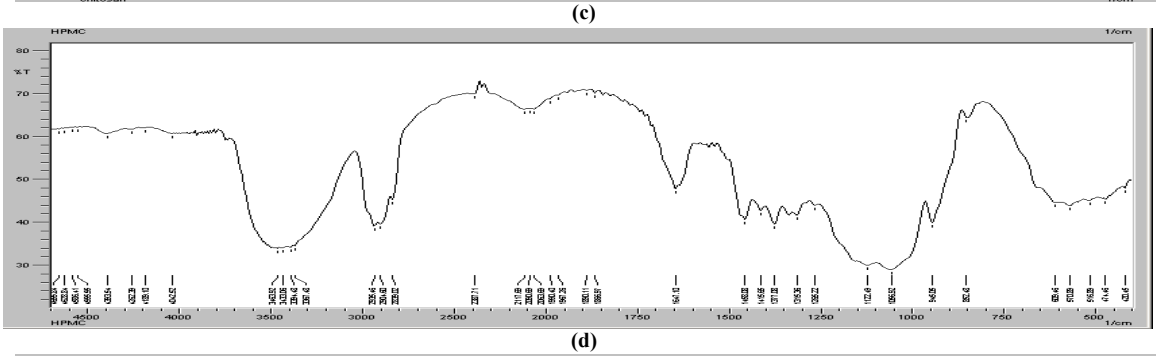
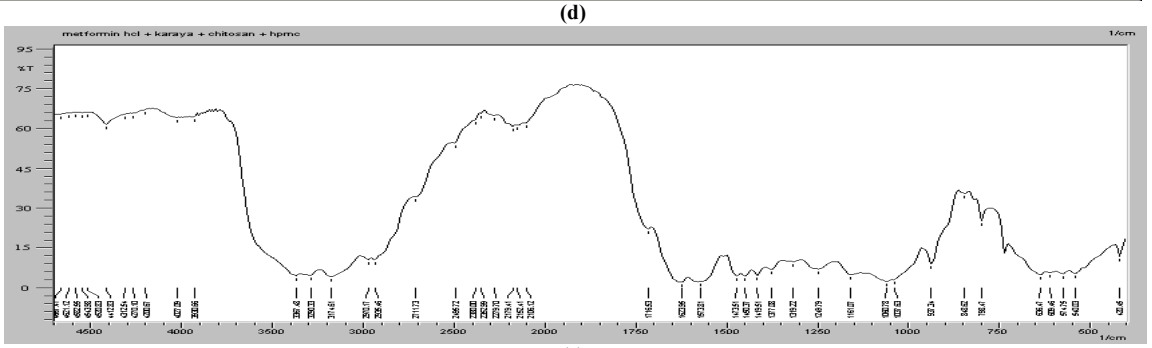


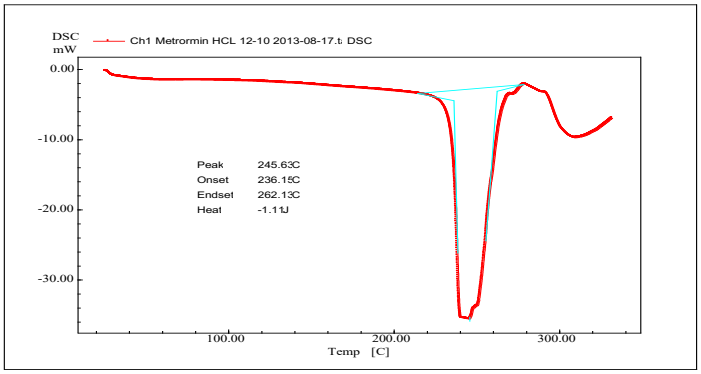
(d)



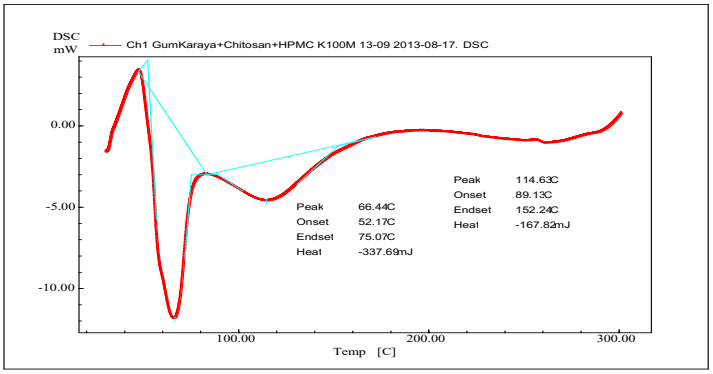
(e)

Figure 7: FTIR spectra of (a) metformin hydrochloride (b) gum karaya (c) chitosan (d) HPMC K100M (e) metformin hydrochloride + gum karaya + chitosan + HPMC K100M

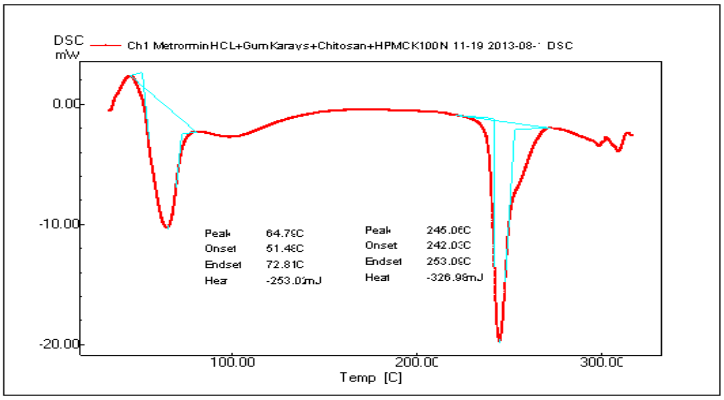
3.5.2. Differential scanning calorimetry



(a)



(b)



(c)

Figure 8: DSC thermograms of (a) metformin hydrochloride (b) gum karaya + chitosan + HPMC K100M (c) metformin hydrochloride + gum karaya + chitosan + HPMC K100M

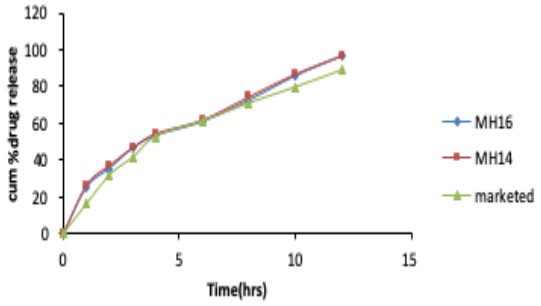


Figure 9: Comparison of *in vitro* drug release of optimized formulations with marketed formulation

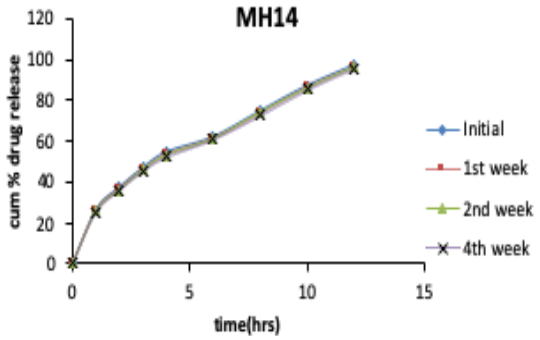


Figure 10: Dissolution profile of optimized formulation MH14

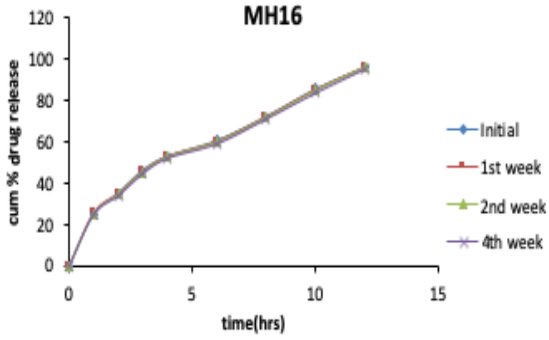


Figure 11: Dissolution profile of optimized formulation MH16

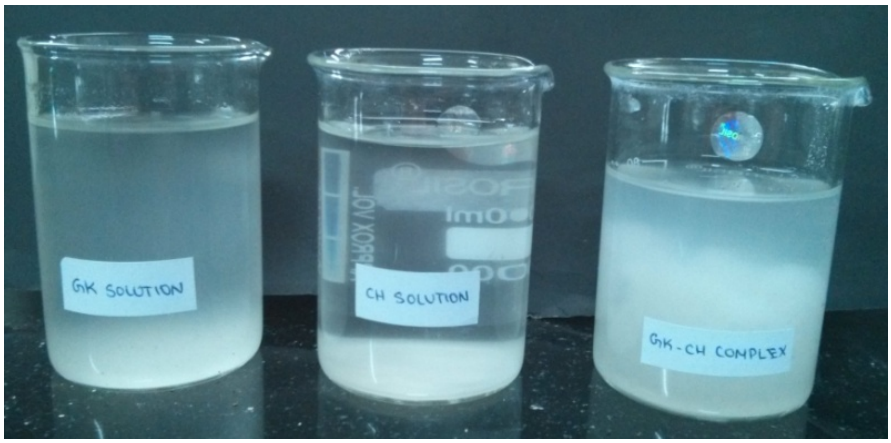


Plate no 1: Polyelectrolyte complex formation between gum karaya and chitosan (GK- gum karaya, CH- chitosan)

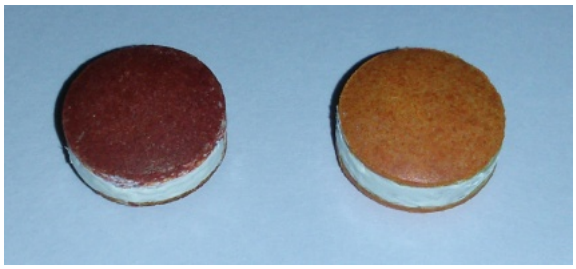


Plate no 2: Tri-layered tablets

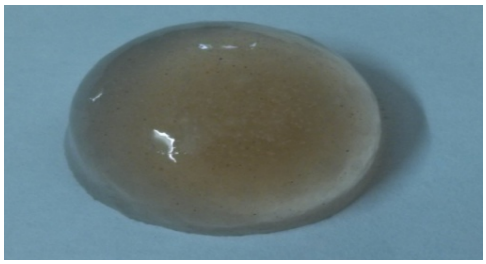


Plate no 3: Swelling of the tablet during dissolution

In this study, during the titration of GK solution with CH solution there is separation of dense phase due to association between the polyelectrolyte polymers (plate no.1). This may lead to neutralization of charge of the polymer. Hence the polyelectrolyte solutions exhibit various pH and conductivity profiles when they interact with each other. In the case of GK and CH, there was a gradual increase in the conductivity of the GK solution from 3.7 mS to 5.8 mS with increasing additions of CH solution. The pH also decreased from 4.44 to 3.97. During the interaction of CH with GK, CH precipitates out of acetic acid solution and this is the reason for increase in the conductivity with decrease in pH. Thus, the pH and conductivity studies clearly indicated the formation of polyelectrolyte complex between CH and GK as shown in Figure 2.

Effect of temperature

The effect of temperature on the formation of PECs was determined at 40 and 60 °C. There was no change in the formation of PECs at 40 and 60 °C, the % yield remained the same.

Evaluation of Prepared Tablets

Evaluation of prepared matrix tablets were conducted and the values for weight variation are in the range of 357 ± 0.79 to 779 ± 0.45 (limits 5% deviation), hardness 6-7 kg/m^2 (I.P limits 4-8), friability 0.11 ± 0.59 to 0.27 ± 0.23 (limits 0.5-1%), thickness 4.18 ± 0.58 to 6.47 ± 0.14 (limits ± 5% deviation), drug content 97.07 ± 0.01 to 99.54 ± 0.21 (limits 95 -105%). This indicates that the evaluation parameters for all the formulations are well within the limits of IP and are given in Table 5.

Sustained release matrix tablets of metformin hydrochloride was formulated by using polyelectrolyte complexes of gum karaya with chitosan, HPMC K100M as layering polymer and magnesium stearate as lubricant by direct compression technique.

Polyelectrolyte complexes of chitosan with gum karaya were prepared in different ratios at chitosan:gum karaya at 1:5, 1:10, 1:15, 1:20 and 1:25. Based on their percentage yield, the ratios 1:10 and 1:15 were selected. As the ratio 1:15 was found to sustain the drug for longer duration as compared to the ratio 1:10, the former ratio was thus taken up for further optimization (Figure 3).

MH1 contains only karaya gum, and from the results it was found that it could sustain the drug for only 6 h. In MH2, MH3 and MH4 contains PECs of chitosan and karaya (1:10). As the PECs concentration was increased drug release decreased slightly. So the ratio of chitosan and karaya of 1:15 was taken in the next formula as shown in Figure 4.

In these MH5 to MH10 it was found that as the concentration of PECs increased, drug release decreased and was sustained till 8 h. It was found that the release patterns for MH9 and MH10 were almost similar, so MH9 was taken up for further optimization as it contained less amount of polymer as compared with MH10.

As PECs could not sustain the drug for more than 8 h, HPMC K 100M was incorporated into the tablet. HPMC K100M in various concentrations (10%, 15%, 20%) was added. HPMC K100M in 15% and 20% sustained the drug release up to 10 h as shown in Figure 5. Instead of further increasing the concentration of HPMCK100M, with their above concentrations tri layered tablets were prepared[13].

It was found that when the tablets containing only drug and PEC were layered with HPMC K100M on top and bottom, in MH14 and MH15, it sustained the release of the drug for 12 h. Similarly layering the tablets with PECs layers on top and bottom in MH16 and MH17 were also able to sustain the release for 12 h. Thus with HPMC K100M and PECs gave sustained release for 12 h, the desired objective of the study was achieved and both the formulations MH14 and MH16 were taken as optimized

formulations (Figure 6). Two typical bands at 3371 cm^{-1} and 3294 cm^{-1}, relative to the N–H primary stretching vibration, and a band at 3170 cm^{-1} due to the N–H secondary stretching, characteristic bands at 1620 cm^{-1} and 1586 cm^{-1} assigned to C-N stretching are observed in the FTIR spectrum of pure metformin hydrochloride as shown in Figure7(a). The IR spectra of GK showed the characteristic peak at 1041 cm^{-1} for ether group, a broad peak at 3417 cm^{-1} due to –OH stretching of the carbohydrate and at 1253 cm^{-1} and 1731 cm^{-1} for acetate group as shown in Figure 7(b). The IR spectra of CH showed a broad peak at 3421 cm^{-1} due to –OH stretching of the carbohydrate and also a peak at 1593 cm^{-1} and 1650 cm^{-1} for –NH group as shown in Figure 7(c). The IR spectrum of the HPMC K100M indicated the characteristics peak of 3453cm^{-1} due to-OH stretching, 2935cm^{-1} due to C-H stretching alkanes and 1122cm^{-1} due to aliphatic C-O stretching as shown in Figure 7(d). It was observed that there was no change in the characteristic peaks of drug in the FTIR spectra as shown in Figure 7(e) suggesting that there were no physical or chemical interactions and functional alteration of drug.

DSC of drug showed an initial flat profile followed by a sharp characteristic endothermic effect, with a Tpeak at 245.6^{o}C, indicating its crystalline state as shown in Figure 8(a). The thermo gram of drug in Figure 8(c) does not show profound shift in peaks indicating compatibility (Tpeak at 245.06^{o}C).

The drug excipient compatibility studies revealed from FTIR and DSC infers that there is no change in the characteristics of drug during the formulation development. The DSC and XRD studies proved that there was retention of the crystalline nature of the drug ruling out any probability of drug and polymer interaction.

Model Dependent Methods

Release kinetics for all the 17 formulations were calculated using Microsoft Office Excel 2007 version. The release data was analyzed by fitting the drug release profiles of all the formulations into zero order release model, first order release model, Higuchi model and Korsmeyer-Peppas model. Regression coefficients (r^2) were calculated for all the formulations. The apparent dissolution rate constant or zero order release constant K_0 was calculated for zero order release model, first order release constant K_1 was calculated for first order release model, Higuchi dissolution constant K_H was calculated for Higuchi model and release exponent n was calculated for Korsmeyer-Peppas model.

Regression coefficients were reported for all the formulations. MH14 and MH16 were considered as optimized formulations on account of their reproducible and promising drug release modulation. The optimized formulations by kinetics (based on the highest r^2 values) followed zero order. The release component "n" was calculated from the Korsmeyer-Peppas kinetics equation which revealed that the formulations followed anomalous transport mechanism in drug release results are given in Table 6.

Comparison of *In Vitro* Drug Release of Optimized Formulations with Marketed Formulation

F1 and F2 for MH14 and MH16 were found to be 10 and 60, 7 and 64 respectively and the comparison profile is shown in Figure 9.

The optimized formulations were compared with the marketed formulation (Glycomet 500 mg SR). As the 250 mg SR tablets are not available the comparison is done using 500 mg SR tablets. The *in vitro* drug release of the marketed formulation at 12th h was found to be 88.73%.

The stability of promising metformin hydrochloride matrix tablets MH14 and MH15 was determined by performing stability studies for one month at accelerated conditions of 40 ± 2^{0}C/75 ± 2% RH. The optimized formulations were found to be stable, with insignificant change in the appearance, hardness, drug content and *in vitro* drug release as given Table 7 and 8 shown in Figure 10 and 11.

CONCLUSION

The tablets were prepared by using gum karaya-chitosan PECs and were layered with HPMC K100M and with polyelectrolyte complexes to obtain sustained release for 12 h. MH14 and MH16 were considered as optimized, where they extended the drug release up to 12 h. The optimized formulations were subjected to stability studies for one month as per ICH guidelines climatic zone III and were found to be stable with insignificant change in the appearance, hardness, drug content and *in vitro* drug release.

To conclude, type II diabetes mellitus can be treated successfully using the prepared optimized formulations MH14 and MH16 for prompt onset of action of drug over a prolonged period of time which may lead to improved efficacy, better patient compliance and avoidance of fluctuations associated with the conventional immediate release formulations.

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