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FORMULATION, EVALUATION AND VALIDATION OF SWELLABLE CONTROLLED RELEASE SYSTEMS OF METFORMIN HYDROCHLORIDE USING NATURAL POLYMERS

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ABSTRACT

Natural polymers such as Chitosan, Acacia, and Pectin were used as matrix forming materials for sustained release formulations. Various formulations of Metformin hydrochloride, as a model drug, were prepared by wet granulation technique with different concentrations of above polymers and complexes of Chitosan-Acacia, Chitosan-Pectin. The granules and tablets were studied for physical properties. In-vitro drug release studies revealed that with the increase in concentrations of polymers, complexes and physical mixtures in the tablets retardation of the drug release also increases. The release of drug from the tablets containing dried complexes was nearly same as those containing physical mixtures. To study the drug release kinetics of examined tablets, the dissolution profiles were analyzed according to zero- order, first-order, higuchi's square root, and peppas korsmeyer's equations. Co-efficient of correlation (r) value was used for the selection of most appropriate model. Formulation F 18 showed 92.34 % of drug release within 12 h and was used for validation studies. Five different batches were prepared and to the results of characterization of granules and tablets one-way ANOVA was applied. All the results show no significant difference and thus the process was validated. Chitosan–Acacia and Chitosan-Pectin polymer complexes can be used as matrix forming materials for the formulation of sustained release Metformin hydrochloride tablets.

Keywords: Sustain Release; Matrix Tablets; Polymers

INTRODUCTION

Natural polysaccharides, gums and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Chitosan has been found useful as a vehicle for sustained release preparations of indomethacin, papaverine hydrochloride and water soluble drug such as propranalol hydrochloride.[1, 2,3] Gum Acacia a dried gummy exudates obtained from stem and branches of various species of Acacia, family-leguminosae has been used as a sustained release carrier.[4] Gabr and Meshali investigated and characterized the possible interaction between the natural cationic (Chitosan) and anionic (Pectin and Acacia) polysaccharides.[5] The solid complexes formed are separated and dried, to be used as tablet matrices. Hence it was intended to use natural polymers such as Chitosan, Acacia and Pectin, as matrix forming material for sustained release formulation of Metformin hydrochloride, a biguanide used in the treatment of non-insulin dependent diabetes mellitus.[6]

MATERIALS

Chitosan was received as a gift sample from C.I.F.T, Kochi, and Metformin Hydrochloride was received as gift sample from RPGT Life Sciences Lab. Mumbai. All other chemicals like Acacia GR grade, Pectin GR grade, Potassium di-hydrogen phosphate AR grade, Potassium chloride AR grade, Glacial acetic acid AR grade are obtained commercially.

EXPERIMENTAL

Preparation of complexes

Mixtures of the polymer solutions, which showed the lowest viscosity, were used in the preparation of the solid complexes. Chitosan solution in 5% acetic acid was mixed with either pectin or acacia solution in distilled

water. The sample solution was then incubated. The supernatant was decanted and the remaining gelatinous complex was dried at 40 °C for 24 hours. The remaining solid complex was further dried under vacuum for 2 days at 37 °C. the dried complexes of Chitosan – pectin and Chitosan − acacia were ground in ball mill and passed through a 100 mesh sieve.

Stoichiometry of the complex: (viscosity measurements)

Chitosan solution in 5% acetic acid was mixed with pectin solution or with acacia solution at constant temperature. The samples solutions was incubated at 37°C for 24 hours, centrifuged for 20 min at 7000 rpm and the viscosity of the supernatant was determined at 37°C.

Confirmation of polymer complex formation

IR spectra of Chitosan, acacia, and pectin, their physical mixtures (Chitosan-acacia and Chitosan-pectin) and also their complexes (Chitosan-acacia and Chitosan-pectin) were carried out.

Preparation of matrix tablets

Tablets were prepared by wet granulation method using 2% acetic acid solution as granulating fluid for tablets prepared by Chitosan alone and complexes and isopropanol for tablets prepared by Acacia and Pectin. Table 1 shows composition of prepared tablets.

Physical Properties

Physical properties of granules were studied by Angle of repose, percentage compressibility, and degree of compression and content uniformity of granules. For study of physical properties of tablets, hardness, friability weight variation, drug content was determined.

In-vitro drug release study

In-vitro drug release was determined using USP XXIII apparatus (basket method). The temperature was maintained at 37± 1^0C at 100 rpm throughout the study. Hydrochloride acid buffer (pH 1.2) was used as dissolution medium for first 2h and alkaline phosphate (pH 6.8) was used for remaining hours. After every hour, 2 ml sample was withdrawn and analyzed spectrophotometrically at 233 nm.

Drug release kinetics

To study of drug release kinetics of examined tablets the dissolution profiles were analyzed according to zero-order, first-order, higuchi's square root and peppas korsmeyer's equations. Co-efficient of correlation (r) value was used for the selection of most appropriate model.

Stability studies

Two separate batches of formulation F18 were kept at room temperature and at 50ºC for 45 days. The tablets were then evaluated for physical properties as well as in vitro drug release.

Validation studies

Formulation F18 was used for validation studies. Five different batches were prepared and studied.

RESULTS AND DISCUSSIONS:

Polymer complexes were prepared and conformed by IR spectra shown in figure 1, 2, 3 and 4. All batches of tablets were produced under similar conditions to avoid processing variables. The compressed tablets were evaluated for various physical parameters. These studies reveal that the tablets formulated were stable.

Results of study of physical properties of granules were shown in table 2.The results of angle of repose indicate good flow properties of the granules. The compressibility index of granules indicates good flow properties of granules. Degree of compression is characteristic of compression capability of the granules and the results obtained exhibited good compression capability of the granules. Degree of homogeneity of blend was studied to evaluate the mixing process. The observation in table indicated uniform mixing.

Results of study of physical properties of tablets were shown in table 3.Table shows that all the tablet formulations showed acceptable pharmacotechnical properties.

Comparative percentage drug release from various formulations of metformin hydrochloride was shown in table 4. In-vitro drug release studies of formulations revealed that formulations F1, F2, F3, composed of drug and chitosan alone in 1:0.75, 1:0.50, 1:0.25 ratios, F4, F5, and F6 composed of drug and acacia and F7, F8, F9 composed of drug and pectin in similar ratios showed relatively fast release. Formulations F10, F11, F12 composed of drug and physical mixture of Chitosan-Acacia in various ratios and formulations F13, F14, F15 composed of drug and physical mixture of Chitosan-Pectin were found to sustain the drug effectively. F10, F11, F12 released 83.26%, 92.38%, and 99.09% drug

after12h, 12h, and 11h respectively, similarly F13, F14, and F15 released 85.80%, 99.31%, and 99.54% drug after 12h, 12h, and 11h respectively. Formulation F16, F17, F18 andF19, F20 and F21 composed of polymer complexes of Chitosan-Acacia and Chitosan-Pectin in different ratios also complexes of Chitosan-Acacia and Chitosan-Pectin in different ratios also showed efficient sustained release. F16, F17, F18 released 77.37%, 83.24%, and 92.34% and F19, F20, F21 released 81.74%, 91.43%, and 99.76% of release up to 12h respectively. It was observed that more the amount of polymer more was the retardation of drug release. The physical mixtures produced tablets with good sustained release, which suggests that inter-polymer complexes were formed during dissolution process.

Table 1: Composition of tablets in each formulation

Formulation	Drug	Chitosan Acacia	Pectin	Chitosan Acacia Physical mixture	Chitosan Pectin Physical mixture	Chitosan Acacia Complex	Chitosan Pectin Complex	Guar gum
F1	500 mg	375 mg						87.5 mg
F2	500 mg	250 mg						75 mg
F3	500 mg	125 mg						62.5 mg
F4	500 mg	375 mg						87.5 mg
F5	500 mg	250 mg						75 mg
F6	500 mg	125 mg						62.5 mg
F7	500 mg		375 mg					87.5 mg
F8	500 mg		250 mg					75 mg
F9	500 mg		125 mg					62.5 mg
F10	500 mg			375 mg				87.5 mg
F11	500 mg			250 mg				75 mg
F12	500 mg			125 mg				62.5 mg
F13	500 mg				375 mg			87.5 mg
F14	500 mg				250 mg			75 mg
F15	500 mg				125 mg			62.5 mg
F16	500 mg					375 mg		87.5 mg
F17	500 mg					250 mg		75 mg
F18	500 mg					125 mg		62.5 mg
F19	500 mg						375 mg	87.5 mg
F20	500 mg						250 mg	75 mg
F21	500 mg						125 mg	62.5 mg

Table 2: Results of study of physical properties of granules of optimized batch

Formulation	Angle of repose (degree)	% Compressibility	Degree of compression	Homogeneity of blend (% w/w)
F10	24.44	19.22	48.75	95.50±1.380
F11	26.68	21.73	47.16	98.01±0.555
F13	25.67	17.85	50.00	93.67±0.448
F16	28.07	23.80	46.20	96.05±0.8125
F18	23.40	16.97	51.23	98.36±0.441
F19	29.05	27.77	45.22	98.80±1.327

Table 3: Results of study of physical properties of tablets of optimized formulations

Formulation	Hardness% (Kg/cm2)	Friability (% w/w)	Weight variation (g)	% Drug content (%w/w)
F10	6-8	0.58	0.9664±0.0036	98.82 ±1.383
F11	6-8	0.72	0.8296±0.0016	96.55±1.165
F13	6-8	0.27	0.9713±0.0032	99.91±1.617
F16	6-8	0.47	0.9674±0.0026	98.33±1.072
F18	6-8	0.56	0.6916±0.0030	97.71±0.704
F19	6-8	0.38	0.9967±0.0039	97.63±0.360

Table 4: Comparative percentage drug release from various formulations of metformin hydrochloride

Time / Formula	1h	2h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	11 h	12 h
F1	39.31	54.26										
F2	46.12	62.37										
F3	40.35	77.44										
F4	65.92	93.89										
F5	37.08	71.66	80.66	89.49	96.38							
F6	25.87	64.60	77.87	81.71	88.46	91.85	97.25					
F7	55.33	74.04	80.71	90.57	94.39							
F8	31.86	64.83	93.40									
F9	23.94	41.65	49.66	59.11	68.21							
F10	19.50	28.13	45.90	53.07	59.56	64.88	67.95	70.29	74.25	78.22	81.01	83.26
F11	24.75	30.85	49.52	57.64	66.87	70.26	75.35	79.27	83.19	86..34	89.86	92.38
F12	28.35	33.78	53.94	60.80	67.56	74.31	80.17	84.45	87.15	93.68	99.09	
F13	15.07	20.94	40.06	46.38	53.00	57.78	62.38	67.33	73.86	77.92	82.42	85.80
F14	15.52	21.84	48.61	49.99	59.67	65.30	73.41	79.94	86.70	92.56	99.31	
F15	16.42	25.44	54.66	59.22	65.52	74.53	80.39	88.27	94.58	99.54		
F16	14.85	21.07	36.73	44.26	49.67	54.85	59.26	62.46	66.56	69.27	73.33	77.37
F17	19.57	23.78	38.40	46.29	57.33	58.24	63.77	66.34	70.62	74.90	79.63	83.24
F18	20.61	24.32	41.64	50.43	60.34	63.96	67.56	71.84	76.57	82.42	87.38	92.34
F19	18.81	24.99	42.31	45.34	52.91	57.42	59.67	68.22	70.93	73.86	77.24	81.74
F20	18.90	26.12	46.73	48.64	56.65	60.72	65.75	71.16	74.77	79.04	85.35	91.43
F21	19.12	29.72	53.57	57.19	61.25	66.43	72.06	78.36	85.12	92.33	99.76	

Table 5: Dissolution kinetics of Metformin hydrochloride

Formulation	Zero order eqn. (r)	1st order eqn. (r)	Higuchi's eqn. (r)	Peppas eqn. (r)
F10	0.8555	0.9883	0.9909	0.9822
F11	0.8557	0.9968	0.9928	0.9849
F13	0.9431	0.9945	0.9841	0.9860
F16	0.9198	0.9940	0.9887	0.9865
F18	0.9245	0.9801	0.9891	0.9853
F19	0.9038	0.9937	0.9931	0.9801

Measuring Mode : xT
Resolution : 4.0 Cm-1
No. of Scan : 40
Gain : Auto
Detector : Detector 1(2.8 mm/sec)
Apodization : Hepp-Genzel
Remarks : Chitosan-Pectin Physical Mixture

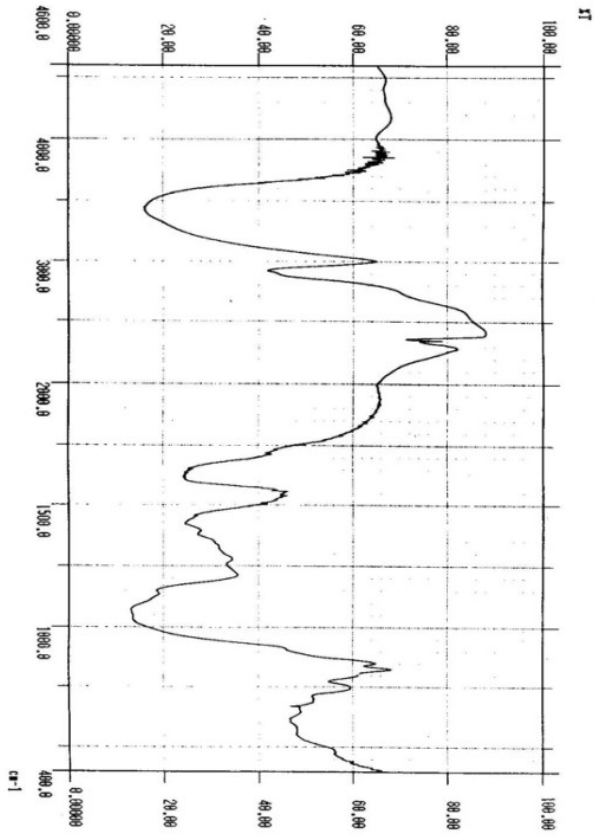

FIGURE 1: IR SPECTRUM OF PHYSICAL MIXTURE OF CHITOSAN, ACACIA

Measuring Mode : xT
Resolution : 4.0 Cm-1
No. of Scan : 40
Gain : Auto
Detector : Detector 1(2.8 mm/sec)
Apodization : Hepp-Genzel
Remarks : Chitosan-Pectin Physical Mixture

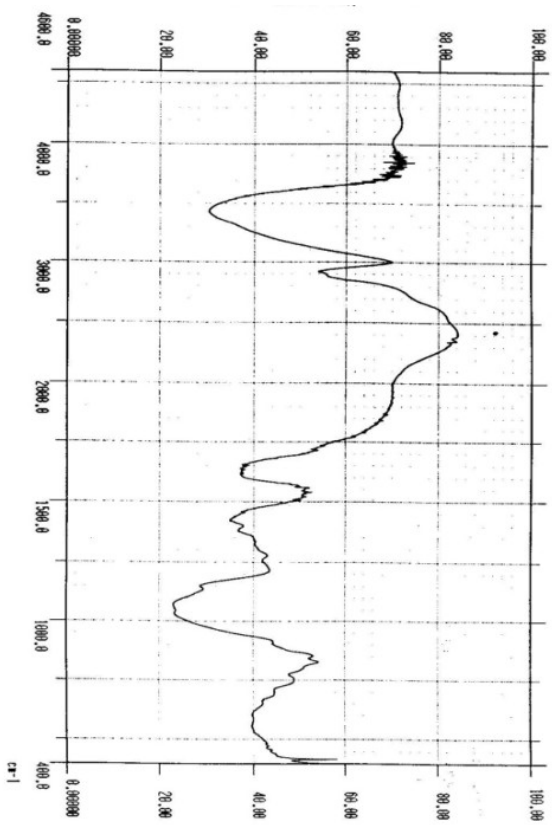

FIGURE 2: IR SPECTRUM OF PHYSICAL MIXTURE OF CHITOSAN, PECTIN

Measuring Mode : xT
Resolution : 4.0 Cm-1
No. of Scan : 40
Gain : Auto
Detector : Detector 1(2.8 mm/sec)
Apodization : Hepp-Genzel
Remarks : Chitosan-Pectin Physical Mixture

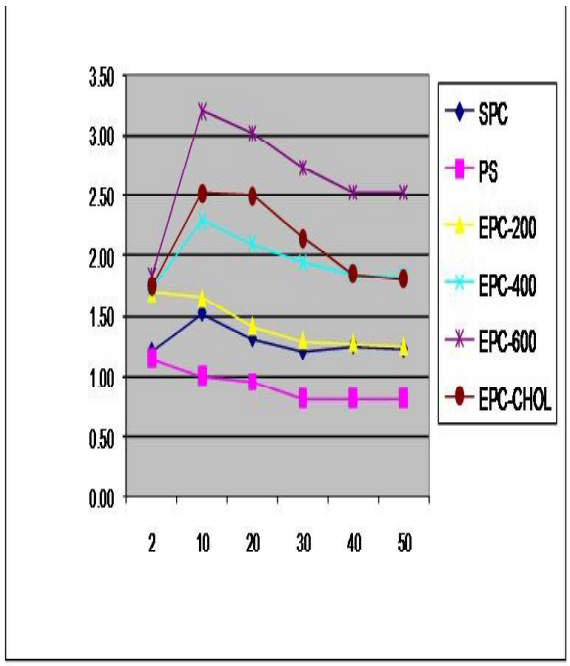

FIGURE 3: IR SPECTRUM OF CHITOSAN- ACACIA COMPLEX

Measuring Mode : xT
Resolution : 4.0 Cm-1
No. of Scan : 40
Gain : Auto
Detector : Detector 1(2.8 mm/sec)
Apodization : Hepp-Genzel
Remarks : Chitosan-Pectin Complex

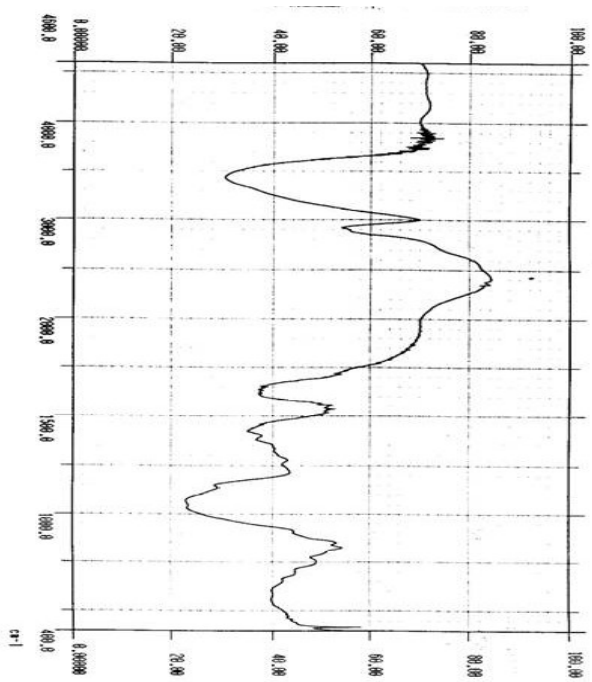

FIGURE 4: IR SPECTRUM OF CHITOSAN, PECTIN COMPLEX

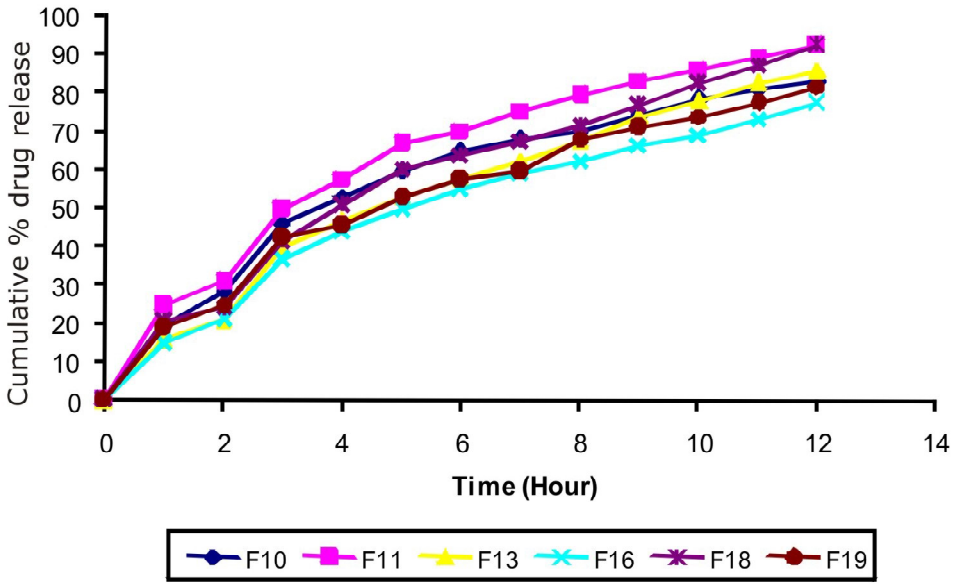

FIGURE 5: FIRST ORDER PLOT

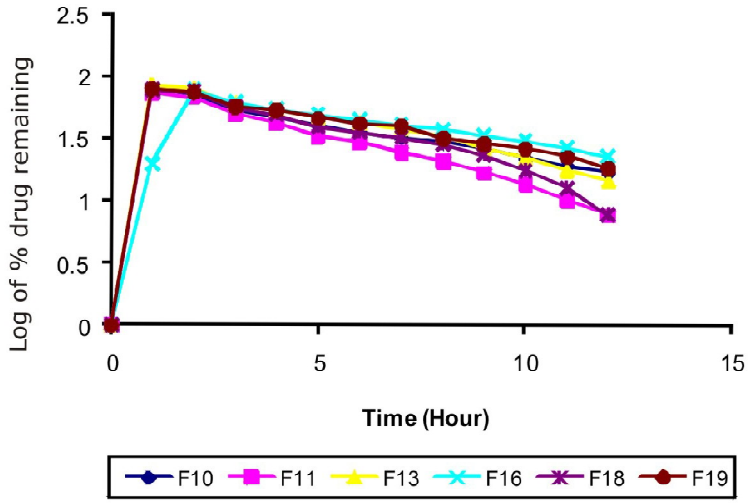

FIGURE 6: ZERO ORDER PLOT

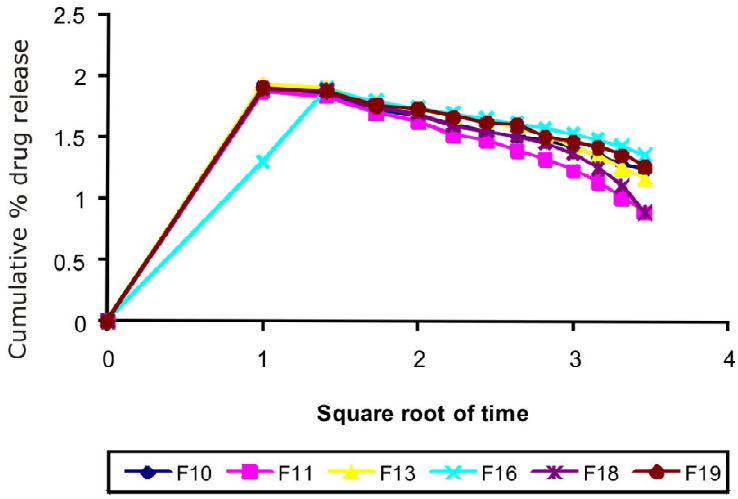

FIGURE 7: HIGUCHI'S PLOT

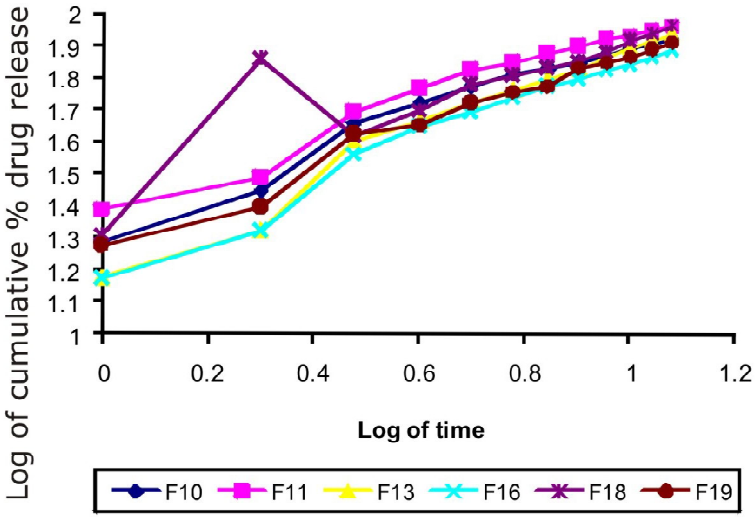

FIGURE 8: PEPPAS KORSMEYER'S PLOT

In order to study the drug release kinetics of the examined tablets, the dissolution profiles of formulations F10, F11, F13, F16, F18 and F19 were analysed according to zero-order, first order, Higuchi's square root and Peppas korsmeyer's equations. (Table 5). Fig. 5, 6, 7 and 8 shows zero order, first order, Higuchi's and Peppas Korsmeyer's plot respectively. From the data it was observed that, the formulations did not follow a zero order release pattern. When the data was plotted according to first order equation, the formulations showed a fair linearity. Release of drug from matrix tablets containing hydrophilic polymers generally involves factors of diffusion and the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square root kinetics or Higuchi′s kinetics. In our study, formulation F11, F13, F16, F19, followed first order release kinetics while F10, F18, followed Higuchi′s equation. To confirm the diffusion mechanism, the data were fit into korsmeyer′s equation, the formulations showed good linearity, indicating that diffusion is dominant mechanism of drug release from these formulations.

From the stability study it was observed that there was no significant change in the physical properties of tablets. Both the batches kept at 37ºC and at 50ºC were found to have 92.08% and 91.56% of drug release after 12 h. Hence, we can say that there were negligible differences in the physical properties as well as drug release pattern of the tablets.

Validation study of formulation F18 containing drug and chitosan-Acacia complex in 1:0.25 ratios was found to release the drug in sustained manner (92.34%) up to 12 hours and was considered optimum for validation studies. Five different batches of formulation F18 were prepared and studied for evaluation of physical properties of granules (angle of repose, percentage compressibility, degree of compression and degree of homogeneity of blend) and tablets (weight variation, friability and content uniformity). To the means of results of physical properties of granules and tablets of different batches, one-way ANOVA test was applied to check the variance between the batches.

CONCLUSION

The study demonstrates that Chitosan- Acacia and Chitosan-Pectin complexes can be used as a matrix forming material for the preparation of sustained release tablets of Metformin hydrochloride.

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