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Formulation and Evaluation of Sustained Release Matrix Tablets of Repaglinide

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Abstract

The aim of present investigation was to formulate and evaluate the sustained release matrix tablets of Repaglinide (RPGN). These matrix tablets were prepared by wet granulation method using synthetic and natural polymers like HPMC K4M, HPMC 100M and Guar gum (GG), Carrageenan (CG), respectively. *In-vitro* drug release studies were performed by USP dissolution apparatus type-II (paddle method) using 0.1 N HCl buffer and pH 6.8 phosphate buffer for 12 h. Amongst all the 12 formulations, formulation F12 showed maximum drug release of 97.9% for 12 h study. It was observed from the kinetic studies that all the formulations followed first order kinetics and particularly the drug release from its dosage form was fickian diffusion (F9, F12), non-fickian diffusion (F1-F8, F10-F11). Formulation F12 was subjected to stability studies and confirmed that formulation F12 was stable upto the period of 1 month.

Key words: Matrix tablets, natural polymers, repaglinide, synthetic polymers, wet granulation

Introduction

The conventional dosage forms such as tablets and capsules are the major oral preparations and have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance in last two decades (Gujar *et al*., 2014).

Repaglinide i.e. (+) 2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)- butyl) amino)-2-oxoethyl) benzoic acid (Harika *et al*., 2013) is an oral antihyperglycemic agent used for the treatment of non insulin dependent diabetes mellitus (NIDDM). It belongs to the meglitinide class of short acting insulin secretagogues, which act by binding to the β cells of the pancreas to stimulate the insulin release (Dasharath *et al*., 2012; Venkataramudu *et al*., 2012). Considerable research had been done on the drug RPGN for sustained release and from the literature, it was found that they were developed bioadhesive buccal drug delivery system (Dasharath *et al*., 2012), effect of Hydroxy propyl-β-cyclodextrin on sustained release bioadhesive buccal tablets (Harika *et al*., 2013), gastroretentive nanoparticles (Gujar *et al*., 2014), matrix systems of Repaglinide using natural polymers (Venkataramudu *et al*., 2012) and synthetic polymers (Joshi *et al*., 2012; Barot *et al*., 2014).

The most commonly using method of modulating the drug release is matrix system (Venkateswarlu and Shanthi, 2012) and an effort was therefore made to develop simple and effective sustained release Repaglinide tablets using a polymer matrix system. From the previous studies, they have developed matrix system using natural polymers like Pectin, Guar gum, Xanthan gum and retarded upto 10 h only (Venkataramudu *et al*., 2012) but incase of synthetic polymers they have retarded upto 12 h (Barot *et al*., 2014). Hence, in the present study, an attempt has been made to develop sustained release matrix tablets of Repaglinide using the synthetic polymers like HPMC K4M, HPMC 100M and natural polymers like Gaur gum, Carrageenan gum and fixed to retard the drug release up to 12 h.

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Materials and Methods

Materials: RPGN was obtained from Active Pharma labs, India and HPMC K4M and HPMC 100M from Yarrow Chemicals, India, GG from Crystal Colloids Ltd., India, CG and PVP from Active Pharma labs, India, Magnesium stearate (MS) and Talc from Merck specialties Pvt. Ltd., India, Lactose from Chemdyes Corporation, India.

Drug excipient compatibility studies: The pure drug and its physical mixtures were subjected to IR spectral studies using FTIR spectrophotometer (Bruker, USA) in the wave number region from 4000 cm^{-1} to 400 cm^{-1}. The spectra obtained for pure drug and the physical mixtures were compared.

Formulation development: Tablets were prepared by wet granulation method using different synthetic and natural polymers like HPMC K4M, HPMC 100M and Guar gum, carrageenan, respectively. Half of the amount of the required quantity of all the ingredients except MS, talc mentioned in table 1 was taken into a mortar and damp mass was prepared by using isopropoyl alcohol as granulating agent. This damp mass was passed through sieve #12 and the granules were dried in an oven at 60 °C for about 30 min and then they were passes through sieve #16. To this remaining half of the quantity of all ingredients and required quantity of MS, talc were added, mixed uniformly. From this mixture, required quantity of the tablet weight was taken and compressed to the tablet using RIMEK rotary tablet punching machine.

Table 1. Preparation of RPGN matrix tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F74	F8	F9	F10	F11	F12
RPGN	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	5	10	15	-	-	-	-	-	-	-	-	-
HPMC 100M	-	-	-	5	10	15	-	-	-	-	-	-
GG	-	-	-	-	-	-	5	10	15	-	-	-
CG	-	-	-	-	-	-	-	-	-	5	10	15
Lactose	130	125	120	130	125	120	130	125	120	130	125	120
MS	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
PVP	1	1	1	1	1	1	1	1	1	1	1	1
Total weight (mg/tablet)	150	150	150	150	150	150	150	150	150	150	150	150

Evaluation studies: The precompression parameters like Bulk density and Tapped density (Shah *et al*., 1997), Angle of repose (Cooper and Gunn, 1986), Compressibility index and Hausner's ratio (USP, 2000) were performed for powder blend and the post-compression parameters like friability, hardness, thickness, weight variation (Banker and Anderson, 1987) were evaluated for the formulated tablets.

Drug Content (Assay): The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements, if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount. Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to average weight of three tablets of RPGN was transferred into a 100 ml volumetric flask containing pH 6.8 Phosphate buffer solution and the volume was made up to the mark. From this, 10 ml solution was taken and shaken by mechanical means using centrifuge at 3000 rpm for 30 min. Then it was filtered through whatman filter paper. From this resulted solution, 1 ml was taken, diluted to 10 ml with pH 6.8 Phosphate buffer and absorbance was measured against blank using UV-Visible spectrophotometer (UV-1800 Spectrophotometer, Shimadzu, Japan) at 237 nm.

In vitro drug release studies: Drug release was assessed by dissolution test and which has been performed by USP type-II dissolution apparatus

(Electro lab TDT-06N USP dissolution apparatus, India) at 50 rpm using 0.1 N HCl buffer and pH 6.8 phosphate buffer for 12 h and temperature was maintained at 37 °C ± 0.5 °C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37 °C ± 0.5 °C) fresh dissolution medium and it was suitably diluted, analyzed by UV-Visible spectrophotometer at 237 nm.

Kinetic analysis of dissolution data: The *in-vitro* drug release data was subjected to various mathematical models for determining the drug release kinetics and drug release mechanism from its dosage form (Dash, 2010).

Stability studies: In the present study, the stability study was performed as per the ICH guidelines at 30 ºC/60% RH and 40 ºC/75% RH for the selected formulation for about 1 month. After specified time intervals, parameters like hardness, drug content and dissolution were evaluated (Kulkarni, 2014; Kanvide and Kulkarni, 2005; Mohrle, 1980).

Results and Discussion

Compatibility studies: On comparison of pure drug FTIR spectra with the spectra of physical mixtures, it was observed that there is no appearance of new peaks and shifting of already existed peaks indicates absence of drug excipients incompatibility (Tables 2, 3, 4 and 5 & Figures 1, 2, 3 and 4).

Micromeritic study: Before preparing the matrix tablets of RPGN, the powder mass was evaluated for flow properties. Hausner's ratio was found to be less than 1.25, indicates good flowability of RPGN powder blends. Carr's index was found in the range of 11.62 to 16.62, indicates that the RPGN powder blends had shown good to fair flowability. Angle of repose was ranged from 31º to 35º, indicates that the RPGN blends possessing good flow properties (Table 6).

Post compression parameters: All the prepared tablets of RPGN were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and fall within the prescribed pharmacopoeial limits of ±10%. The hardness of the tablet formulations was found to be in

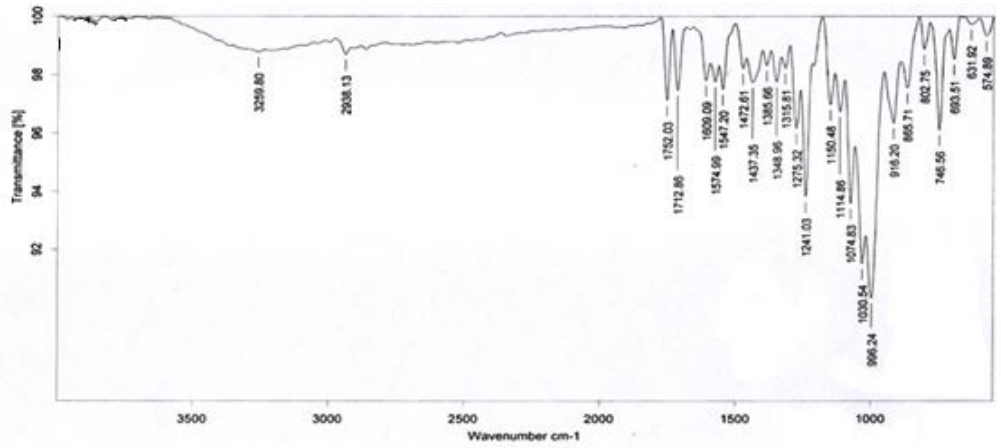

Figure 1. FTIR spectra of pure RPGN.

Table 2. Interpretation of IR spectra of pure RPGN.

Sample	Wave number (cm^{-1})		Functional group
	Range	Observed	
RPGN	~3300	3250	-C = C-H (str)
	2960-2850	2938	-C-H (str)
	~1788	1752	-C=O cyclobutanone (str)
	1610-1550	1547	-C=O carboxylate anion (str)
	1550-1510	1542	-N-H 2^0 amide

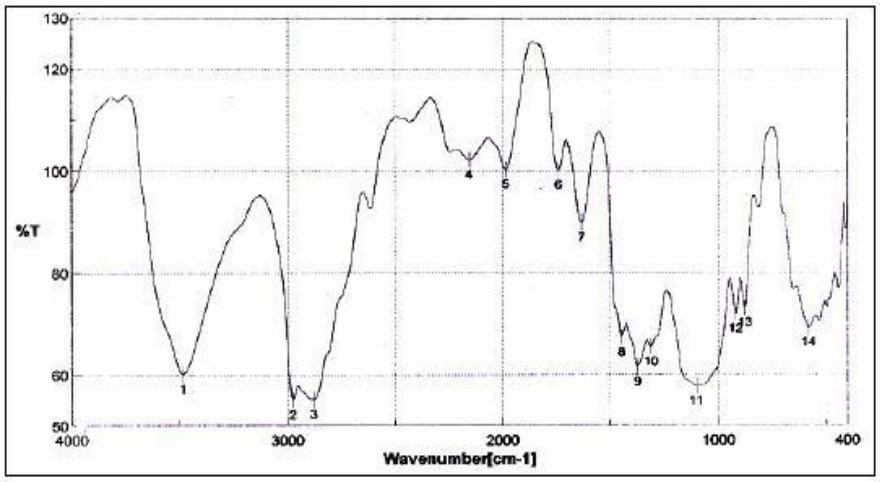

Figure 2. FTIR spectra of RPGN + HPMC.

Table 3. Interpretation of IR spectra of RPGN + HPMC.

Sample	Wave number (cm^{-1})		Functional group
	Range	Observed	
RPGN + HPMC	~3300	3360	-C = C-H (str)
	2960-2850	2940	-C-H (str)
	~1788	1762	-C=O cyclobutanone (str)
	1610-1550	1550	-C=O carboxylate anion (str)
	1550-1510	1542	-N-H 2° amide

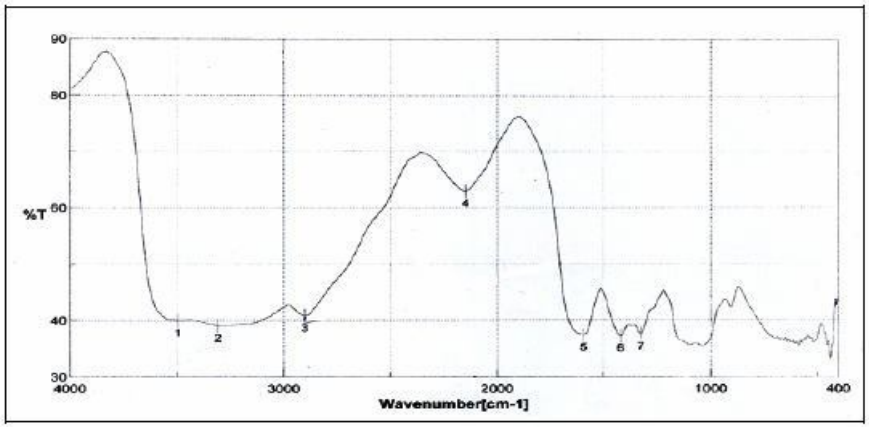

Figure 3. FTIR spectra of RPGN + GG.

Table 4. Interpretation of IR spectra of RPGN + GG.

Sample	Wave number cm^{-1}		Functional group
	Range	Observed	
RPGN + GG	~3300	3280	-C = C-H (str)
	2960-2850	2880	-C-H (str)
	~1788	1762	-C=O cyclobutanone (str)
	1610-1550	1550	C=O carboxylate anion (str)
	1550-1510	1543	-N-H 2^0 amide

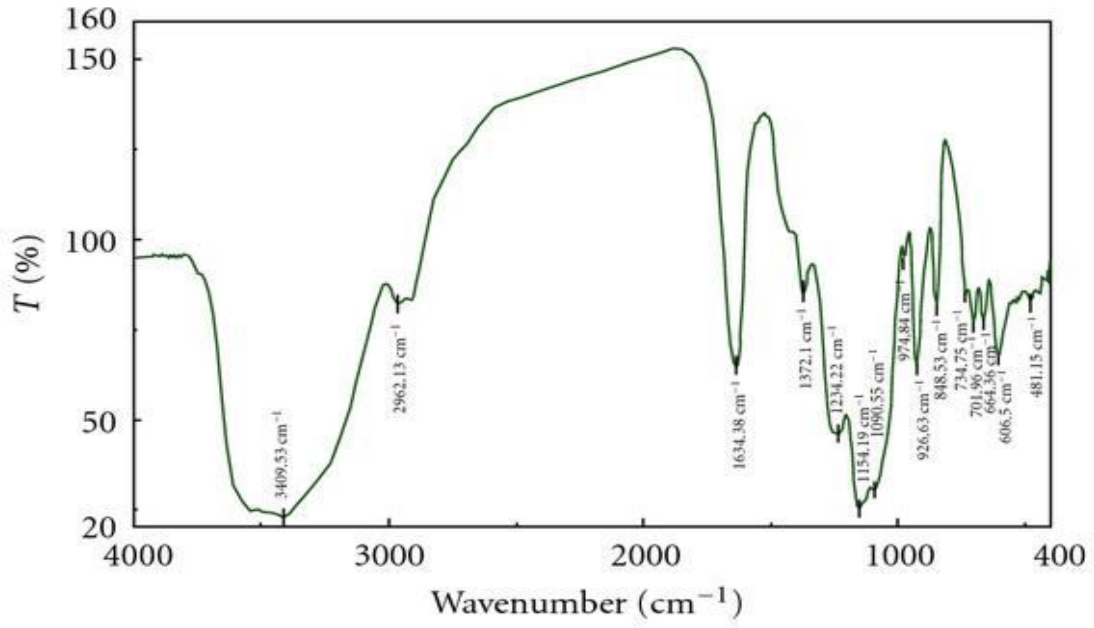

Figure 4. FTIR spectra of RPGN + CG.

Table 5. Interpretation of IR spectra of RPGN + CG.

Sample	Wave number cm^{-1}		Functional group
	Range	Observed	
RPGN + CG	~3300	3409	-C = C-H (str)
	2960-2850	2962	-C-H (str)
	~1788	1634	-C=O cyclobutanone (str)

Table 6. Precompression studies.

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.55 ± 0.12	0.65 ± 0.89	12.2	1.21 ± 0.87	t23.45 ± 0.0002
F2	0.54 ± 0.31	0.62 ± 0.781	13.1	1.22 ± 0.67	19.65 ± 0.0055
F3	0.56 ± 0.41	0.64 ± 0.65	14.5	1.23 ± 0.45	22.35 ± 0.0063
F4	0.54 ± 0.54	0.63 ± 0.51	14.1	1.24 ± 0.39	20.69 ± 0.0074
F5	0.50 ± 0.84	0.64 ± 0.45	12.3	1.22 ± 0.59	20.82 ± 0.0041
F6	0.53 ± 0.78	0.64 ± 0.32	13.4	1.23 ± 0.43	20.72 ± 0.0056
F7	0.51 ± 0.97	0.67 ± 0.21	14.6	1.24 ± 0.48	20.89 ± 0.0049
F8	0.52 ± 0.64	0.62 ± 0.91	14.7	1.21 ± 0.57	20.76 ± 0.0058
F9	0.56 ± 0.53	0.61 ± 0.87	12.3	1.22 ± 0.56	22.61 ± 0.0041
F10	0.52 ± 0.72	0.66 ± 0.74	13.3	1.21 ± 0.42	22.32 ± 0.0039
F11	0.51 ± 0.89	0.62 ± 0.68	14.6	1.24 ± 0.32	24.64 ± 0.0087
F12	0.57 ± 0.99	0.68 ± 0.54	15.1	1.25 ± 0.12	25.83 ± 0.0094

Results were expressed in Avg ± SD (n=3)

Table 7. Post compression studies.

Formulations	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	1.44 ± 0.21	5.12 ± 0.124	3.221 ± 0.0038	0.321 ± 0.21
F2	1.41 ± 0.24	5.23 ± 0.25	3.342 ± 0.0041	0.421 ± 0.32
F3	1.40 ± 0.31	5.27 ± 0.27	3.351 ± 0.0042	0.432 ± 0.12
F4	1.41 ± 0.34	5.31 ± 0.31	3.367 ± 0.0044	0.471 ± 0.41
F5	1.42 ± 0.36	5.26 ± 0.33	3.371± 0.0045	0.512 ± 0.54
F6	1.46 ± 0.41	5.32 ± 0.34	3.372 ± 0.0047	0.653 ± 0.32
F7	1.47 ± 0.45	5.48 ± 0.35	3.381 ± 0.0041	0.782 ± 0.56
F8	1.45 ± 0.35	5.44 ± 0.36	3.383 ± 0.0042	0.861 ± 0.37
F9	1.44 ± 0.63	5.55 ± 0.33	3.394 ± 0.0048	0.751 ± 0.87
F10	1.48 ± 0.55	5.46 ± 0.38	3.395 ± 0.0044	0.573 ± 0.67
F11	1.46 ± 0.45	5.47 ± 0.36	3.397 ± 0.0043	0.524 ± 0.94
F12	1.47 ± 0.56	5.49 ± 0.37	3.397 ± 0.0045	0.681 ± 0.65

Results were expressed in Avg ± SD (n=3)

the range of 4 to 5 kg/cm^2. The friability values were found to be in the range of 0.50 to 0.75%. All the formulations showed less than 1% friability ensuring that the tablets were mechanically stable (Table 7).

Drug content: The low values of standard deviation indicate uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 97.3 to 101.1 percent (which was within the acceptable limits of ±5%).

In vitro dissolution study: Formulations F1, F2 and F3 were prepared by using 5 mg, 10 mg and 15 mg of HPMC K4M and the drug release was found to be 74.3%, 82.3% and 87.5% within 6 h, 7 h, 8 h, respectively. Formulations F4, F5 and F6 were prepared by using 5 mg, 10 mg and 15 mg of HPMC 100M and the drug release was found to be 83.6%, 87.3% and 92.3% within 7 h, 8 h, 9 h, respectively. Formulations F7, F8 and F9 were prepared by using 5 mg, 10 mg and 15 mg of GG and the drug release was found to be 88.5%, 91.5% and 93.6% within 9 h respectively. Formulations F10, F11and F12 were prepared by using 5 mg, 10 mg and 15 mg of CG and the drug release was found to be 93.2%, 95.2% and 97.5% respectively. The dissolution rate was found to be increased linearly with the increase in concentration of polymer i.e. the polymer concentration is directly proportional to the drug release rate. Amongst all the formulations, Tablets prepared with CG showed sustained release of drug upto 12 h especially F11 and F12 but the formulation F12 showed maximum cumulative percent drug release (C%DR) than F11(Table 8).

Table 8. *In-vitro* drug release studies of RPGN tablets (F1-F12).

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	22.6 ± 0.21	26.9 ± 0.32	29.4 ± 0.44	25.1 ± 0.54	29.8 ± 0.64	33.1 ± 0.51	27.1 ± 0.44	31.5 ± 0.46	36.2 ± 0.15	29.6 ± 0.53	33.2 ± 0.64	37.5 ± 0.51
2	31.4 ± 0.12	35.2 ± 0.71	41.2 ± 0.61	36.5 ± 0.63	41.2 ± 0.57	46.7 ± 0.47	38.3 ± 0.12	41.3 ± 0.75	45.3 ± 0.74	40.3 ± 0.22	47.8 ± 0.73	51.3 ± 0.47
3	46.1 ± 0.47	51.2 ± 0.54	54.2 ± 0.81	48.7 ± 0.42	52.2 ± 0.49	57.2 ± 0.58	49.3 ± 0.26	53.3 ± 0.94	59.4 ± 0.85	52.4 ± 0.62	57.4 ± 0.49	59.5 ± 0.58
4	53.2 ± 0.57	62.2 ± 0.21	67.5 ± 0.85	57.5 ± 0.35	61.2 ± 0.55	68.1 ± 0.62	59.4 ± 0.53	61.8 ± 0.59	66.2 ± 0.26	60.7 ± 0.35	66.2 ± 0.99	69.5 ± 0.62
5	66.4 ± 0.77	72.3 ± 0.58	76.5 ± 0.63	69.6 ± 0.58	72.3 ± 0.61	75.2 ± 0.74	71.3 ± 0.85	76.7 ± 0.16	79.2 ± 0.47	72.2 ± 0.58	76.1 ± 0.61	79.4 ± 0.74
6	74.3 ± 0.73	78.4 ± 0.52	81.1 ± 0.32	77.8 ± 0.61	81.7 ± 0.72	83.5 ± 0.87	79.4 ± 0.16	83.2 ± 0.27	86.2 ± 0.78	81.7 ± 0.61	83.2 ± 0.72	86.3 ± 0.87
7	74.3 ± 0.59	82.6 ± 0.91	85.6 ± 0.41	83.6 ± 0.55	86.8 ± 0.81	88.8 ± 0.92	82.2 ± 0.47	85.2 ± 0.18	89.2 ± 0.29	85.3 ± 0.74	87.2 ± 0.81	89.2 ± 0.92
8	74.6 ± 0.28	82.2 ± 0.38	87.3 ± 0.98	83.2 ± 0.43	87.3 ± 0.93	90.4 ± 0.88	85.3 ± 0.34	88.3 ± 0.93	90.3 ± 0.86	87.4 ± 0.43	89.4 ± 0.39	91.4 ± 0.68
9	74.7 ± 0.99	82.5 ± 0.85	87.6 ± 0.24	83.5 ± 0.71	87.1 ± 0.65	92.7 ± 0.22	88.5 ± 0.17	91.5 ± 0.56	93.6 ± 0.25	93.2 ± 0.71	92.1 ± 0.65	95.2 ± 0.52
10	74.3 ± 0.56	82.7 ± 0.81	87.4 ± 0.53	83.1 ± 0.68	87.4 ± 0.81	92.3 ± 0.39	88.4 ± 0.93	91.2 ± 0.84	93.4 ± 0.93	93.8 ± 0.98	95.2 ± 0.48	97.6 ± 0.39
11	74.1 ± 0.77	82.9 ± 0.98	87.5 ± 0.89	83.7 ± 0.59	87.8 ± 0.71	92.1 ± 0.57	88.2 ± 0.46	91.3 ± 0.75	93.2 ± 0.75	93.5 ± 0.64	95.3 ± 0.71	97.7 ± 0.57
12	74.0 ± 0.87	82.3 ± 0.52	87.3 ± 0.75	83.8 ± 0.66	87.3 ± 0.41	92.8 ± 0.66	88.1 ± 0.77	91.6 ± 0.49	93.1 ± 0.64	93.3 ± 0.57	95.4 ± 0.46	97.9 ± 0.46

Kinetics study of RPGN formulations (F1-F12): *In-vitro* drug release data of all the sustained release formulations was subjected to goodness of fit test by linear regression analysis according to the zero order and first order kinetic equations and Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients were summarized in table 9. From this regression coefficient data, it can be seen that all the formulations have displayed first order release kinetics ('r^2' values in the range of 0.900 to 0.965). From Higuchi and Peppas data, it was evident that the drug was released from its dosage form by non-fickian diffusion mechanism in the case of formulations F1-F8 and F10-F11 but formulations F9 and F12 showed fickian diffusion mechanism (Table 9).

Table 9. Release kinetics data of all the formulations.

Formulation code	Zero order	First order	Higuchi	Peppas	Drug release mechanism
	R^2	R^2	R^2	n	
F1	0.977	0.978	0.970	0.681	Non-fickian
F2	0.948	0.992	0.974	0.681	Non-fickian
F3	0.905	0.992	0.989	0.552	Non-fickian
F4	0.966	0.985	0.984	0.653	Non-fickian
F5	0.928	0.985	0.992	0.550	Non-fickian
F6	0.881	0.994	0.992	0.485	Non-Fickian
F7	0.918	0.991	0.989	0.569	Non-fickian
F8	0.99	0.986	0.987	0.521	Non-fickian
F9	0.873	0.985	0.987	0.446	Fickian
F10	0.921	0.979	0.993	0.546	Non-fickian
F11	0.862	0.996	0.987	0.464	Non-Fickian
F12	0.791	0.991	0.959	0.397	Fickian

Table 10. Evaluation of formulated F12 tablets after 1 month of stability study.

Parameters	30 °C/60% RH	40 °C/75% RH
Hardness (kg/cm^2)	4.5	4.6
Drug content (%)	96.43	97.58

Table 11. C%DR of F12 formulation subjected to stability studies at 30 °C/60% RH and 40 °C/75% RH for 1 month.

Time intervals (h)	C%DR of F12		
	30 °C/60% RH (After 1 month)	40 °C/75% RH (After 1 month)	F12 (Dissolution study- 37 °C ± 0.5 °C)
0	0	0	0
1	38.2 ± 0.43	39.8 ± 0.74	37.5 ± 0.51
2	52.4 ± 0.76	53.3 ± 0.31	51.3 ± 0.47
3	60.5 ± 0.58	62.8 ± 0.39	59.5 ± 0.58
4	69.9 ± 0.49	68.6 ± 0.43	69.5 ± 0.62
5	80.4 ± 0.43	80.8 ± 0.53	79.4 ± 0.74
6	87.3 ± 0.78	86.3 ± 0.79	86.3 ± 0.87
7	89.9 ± 0.39	90.2 ± 0.91	89.2 ± 0.92
8	91.7 ± 0.45	92.5 ± 0.69	91.4 ± 0.68
9	96.4 ± 0.57	94.2 ± 0.61	95.2 ± 0.52
10	97.7 ± 0.81	96.8 ±0.46	97.6 ± 0.39
11	97.9 ± 0.84	98.5 ± 0.51	97.7 ± 0.57
12	98.7 ± 0.73	99.7 ± 0.49	97.9 ± 0.46

Stability studies: After stability study period of 1 month, the selected F12 tablets were evaluated for the post compression parameters like hardness, drug content and *in-vitro* drug release. From the results, it was evident that there was no significant change occurs in the above parameters. The C% DR of F12 was compared with the C% DR after stability studies and it was observed that there was no significant change occurs in C% DR (Tables 10 and 11).

Conclusion

It could be concluded from the results, that the tablets consist of the polymer carrageenan showed sustained release upto 12 h, especially the formulation F12. In the previous studies, they have retarded the drug release up to 10 h using natural polymer Pectin (Venkataramudu *et al*., 2012) but in this study, extended the drug release up to 12 h using the natural polymer Carrageenan gum. Kinetic studies confirmed that all the formulations follows first order kinetics and mechanism involved in drug release from its dosage form was fickian diffusion (F9, F12), non-fickian diffusion (F1-F8, F10-F11). Formulation F12 was subjected to stability studies and confirmed that the formulation F12 stable upto the period of 1 month. Success of the i*n-vitro* drug release studies recommends the product for further *in-vivo* studies, which may improves the patient compliance.

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