International Journal of Farmacia

Journal Home page: www.ijfjournal.com

Preparation and evaluation of sustained release matrix tablets of Repaglinide (USP) using natural polymers

Mahmooda*, 'Dr. Syed abdul azeez basha

Deccan college of pharmacy, Darussalam, Aghapura, Nampally, Telangana Hyderabad

***Corresponding author: 'Dr. Syed abdul azeez basha**

Email id: ahmoodashaik21@gmail.com

ABSTRACT

The objective of the present work is to develop and characterizes oral sustain release matrix tablets of Repaglinide. Repaglinide is practically insoluble in water so it is suitable to develop sustained release matrix tablet using hydrophilic polymers. Repaglinide is anti-diabetic drug used extensively in the treatment of diabetes type II. The natural polymers like carrageenan, chitosan, gum karaya, Bhara gum were utilized in the formulation of matrix tablets containing Repaglinide by wet granulation technique and evaluated for its drug release characteristics. Granules were prepared and evaluated for its physical properties and shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in vitro* drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The *in vitro* release study of matrix tablets were carried out in phosphate buffer pH 6.8 for 12 hr. Among all the formulations, F2 with shows 100% better controlled release at the end of 12 hrs when compared to other formulations. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero order to evaluate the kinetics and mechanism of the drug release. The drug release of optimized formulations F2 follows zero order kinetics and the mechanism was found to be diffusion coupled with erosion (non-Fickian diffusion). The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Keywords: Repaglinide, chitosan, Carrageenan, Gum karaya, bhara Gum, Matrix tablet, Sustained release, Wet granulation.

INTRODUCTION

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system [34, 35]. Recent trend in development of sustained-release drug delivery systems was the use of gums of plant origin to fulfill the aim of retarding the drug release [1, 21]. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form [27, 28]. Repaglinide is the first member of new class of oral hypoglycemic designed to normalize the [29, 30] meal time glucose excursions. Repaglinide induces rapid onset short lasting insulin release [23, 24]. It is administered before each major meal to control postprandial hyperglycemia the [36- 37] dose may be omitted if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycemia [2]. Side effects are mild headache, dyspepsia, arthralgia, and weight gain [25, 26]. After oral administration, Repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses inn healthy subjects or in patients, [32, 33] peak plasma drug levels (Cmax) occurs within 1 hour (Tmax) [3, 22]. The present study was [38, 39] designed to formulate matrix tablets using carrageenan, chitosan, gum

karaya, bhara gum matrix polymers for controlling release of poorly water soluble drug Repaglinide.

AIM AND OBJECTIVE

Aim

The main aim of the present investigation is to design, formulate and evaluate the sustained release dosage form of Repaglinide (USP) using natural polymers [4, 31].

Objectives

1. Preformulation studies such as API characterization, solubility studies, determination of melting point.
2. To improve its oral bioavailability.
3. To develop the extended release system over a period of time.
4. Increased patient compliance by reducing the dose frequency.
5. Determination of $\lambda_{max\ and}$ development of calibration curve of Repaglinide using UV spectrophotometer.
6. To perform various quality control evaluation parameters for the prepared tablets.

METHODOLOGY

Formulation of extended release layer

Matrix tablets of were prepared by Wet Granulation method [5, 6]. The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve. Repaglinide, Carrageenan [7,8], Chitosan, Bhara gum, gum karaya, Ethyl cellulose, Micro crystalline cellulose were taken in a poly bag according to the formulation table and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug [9,10]. Weigh Starch accurately [40] and it is mixed with water to form a paste is used as binder solution and kept separately [11, 12]. The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules [13, 14]. Then the wet granules were dried in trays and pass the air for drying .Samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content [15, 16]. The dried materials were passed through the sieve#20. After sieving dry granules were lubricated using Magnesium .stearate and Talc [17, 18]. After lubrication granules were sent to compression. Repaglinide Matrix tablets was compressed using 12mm round punch [19, 20].

Table 1: Formulation table for extended release layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Repaglinide (USP)	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg
Carrageenan	15%	30%	-	-	-	-	-	-
Chitosan	-	-	15%	30%	-	-	-	-
Bhara gum	-	-	-	-	15%	30%	-	-
Gum karaya	-	-	-	-	-	-	15%	30%
Starch	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Talc	12mg	12mg	12mg	12mg	12mg	12mg	12mg	12mg
Ethyl cellulose	30mg	60mg	30mg	60mg	30mg	60mg	30mg	60mg
Magnesium Stearate	12mg	12mg	12mg	12mg	12mg	12mg	12mg	12mg
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total wt (mg)	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

Preformulation studies

Organoleptic characters for Repaglinide

Description of Repaglinide

Test	Description
Colour	white to off-white powder

Solubility

Solvents	Solubility
Water	Practically insoluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Ethanol	Soluble

Melting point

Melting point of Repaglinide drug was determined by using melting point apparatus and was in the range of 131^{o}C.

Evaluation of repaglinde tablets

Table 2: Precompession parameters

Formulations	Bulk Density(gm/ml)	Tapped density(gm/ml)	Carr's Index (%)	Hausner ratio	Angle of repose (^{0})
F1	0.356	0.400	11.00	1.12	28.16
F2	0.379	0.429	11.66	1.13	24.59
F3	0.344	0.392	12.24	1.14	28.73
F4	0.369	0.425	13.18	1.15	25.14
F5	0.373	0.429	13.05	1.15	27.35
F6	0.349	0.410	14.88	1.17	28.19
F7	0.371	0.426	12.91	1.15	26.31
F8	0.396	0.453	12.58	1.14	25.14

The blends for Matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausners ratio. Angle of repose was less than 30° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flowability and compressibility. Hausner's ratio was less than 1.17 for all the batches indicating excellent flow properties.

Table 3: Post compression parameters

F.Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)
F1	5.4 ±0.44	2.08±0.17	199.8±1.48	0.36
F2	4.5±0.31	2.70±0.25	200.4±0.54	0.39
F3	5.5±0.40	2.81±0.80	198.6±0.41	0.43
F4	5.5±0.55	2.2±0.20	200.8±1.64	0.12
F5	4.6±0.57	2.08±0.66	205.6±1.14	0.54

F6	5.0±0.30	2.91±0.25	199.2±0.83	0.58
F7	4.5±0.57	2.1±0.71	199.9±0.67	0.64
F8	5.4±0.60	2.0±0.89	199.0±0.43	0.37

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in above Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 198.6±0.41 and 200.8±1.64mg. The hardness of the tablets ranged from 4.5±0.31 to 5.5±0.55 kg/cm^2 and the friability values were less than 0.65% indicating that tablets were compact and hard. The thickness of the tablets ranged from 2.0 to 2.91 mm. All the formulations satisfied the content of the drug as they contained 98 to 100 % of Repaglinide and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Invitro dissolution studies for matrix tablets

Dissolution study (matrix tablets)

Acidic Stage

Medium : 0.1N HCL
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Temperature : 37ºC± 0.5
Time : 2hrs

Buffer Stage

Medium : 6.8pH phosphate buffer
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Time : 12hrs.

Table 4: Cumulative percentage drug release from matrix tablets

Time (hrs)	F1 %drug release	F2 %drug release	F3 %drug release	F4 %drug release	F5 %drug release	F6 %drug release	F7 %drug release	F8 %drug release
Dissolution medium 0.1N HCL								
0.5	7.2	3.1	4.5	3.1	5.1	4.8	5.8	5.1
1	11.8	6.5	9.2	8.3	7.4	8.7	8.6	9.8
2	20.6	12.4	18.6	10.8	8.7	15.7	12.3	15.4
6.8pH phosphate buffer								
3	29.1	21.8	20.8	21.6	28.0	19.8	17.8	20.9
4	33.8	26.8	33.4	28.7	37.6	23.8	22.8	27.6
5	40.8	30.9	41.8	34.3	43.8	31.7	26.6	30.8
6	45.6	36.8	50.3	46.8	51.4	36.8	31.8	36.4
7	54.3	39.2	58.6	49.2	63.4	43.2	39.3	41.8
8	63.4	48.3	64.5	55.8	75.4	49.6	46.9	49.1
9	71.8	55.8	73.8	61.3	75.4	51.6	51.8	54.6
10	80.6	65.6	81.7	66.8	89.6	57.8	65.3	59.4
11	87	85.6	88	87.3	93.1	83.6	76.6	65.3
12	91	100	94.2	91	97	89.8	83.6	71.6

The Formulation F2 showed 100% drug release at 12 hrs.

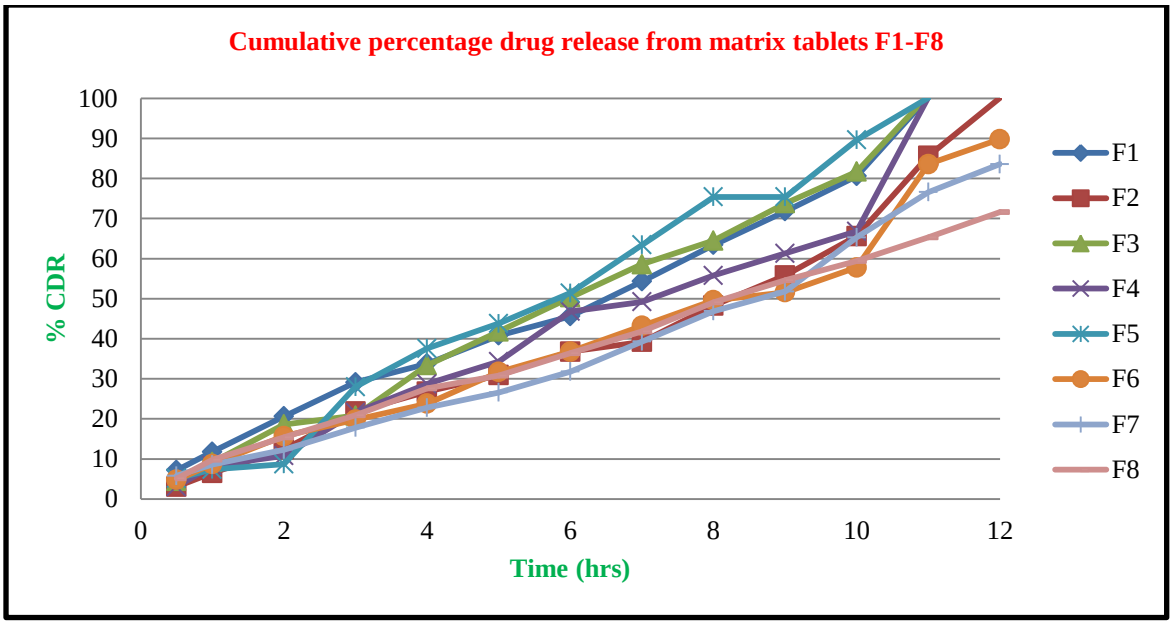

Fig 1: In-Vitro Drug Release Studies for matrix tablets F1 – F8.

Release kinetics of F2

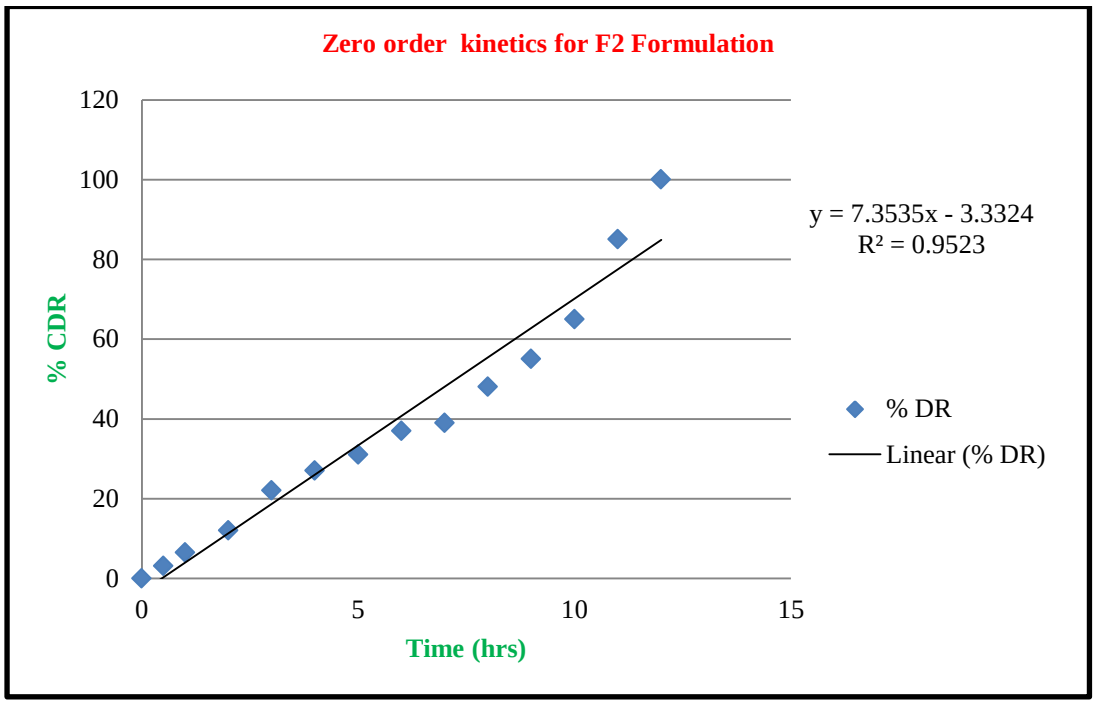

Fig 2: Zero order graph for F2 Formulation

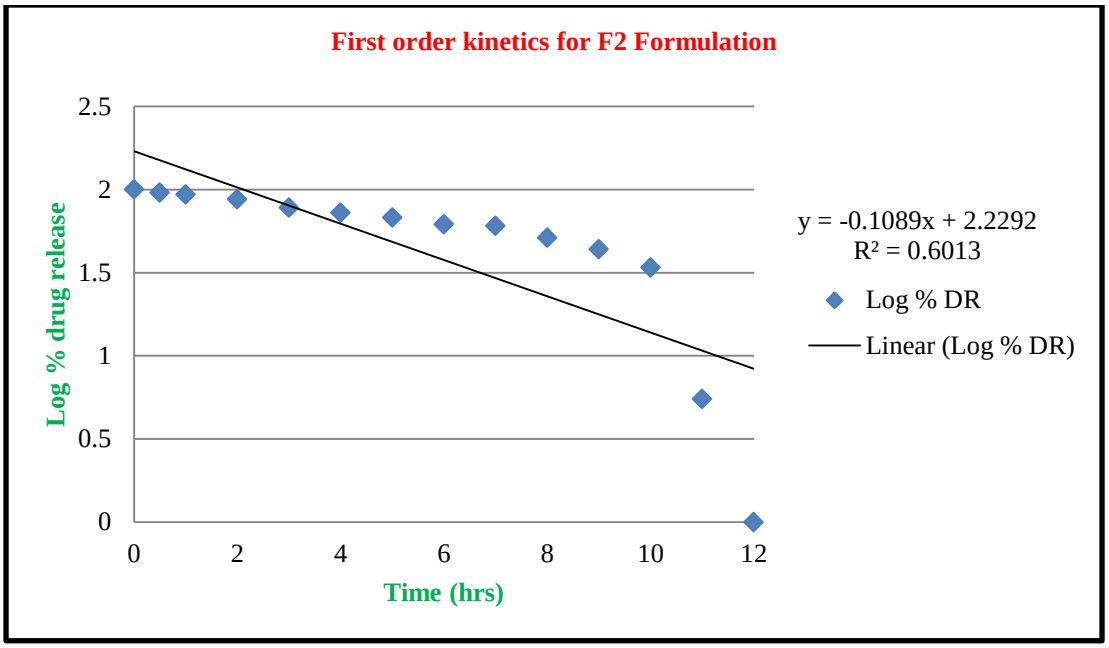

Fig 3: First order graph for F2 Formulation

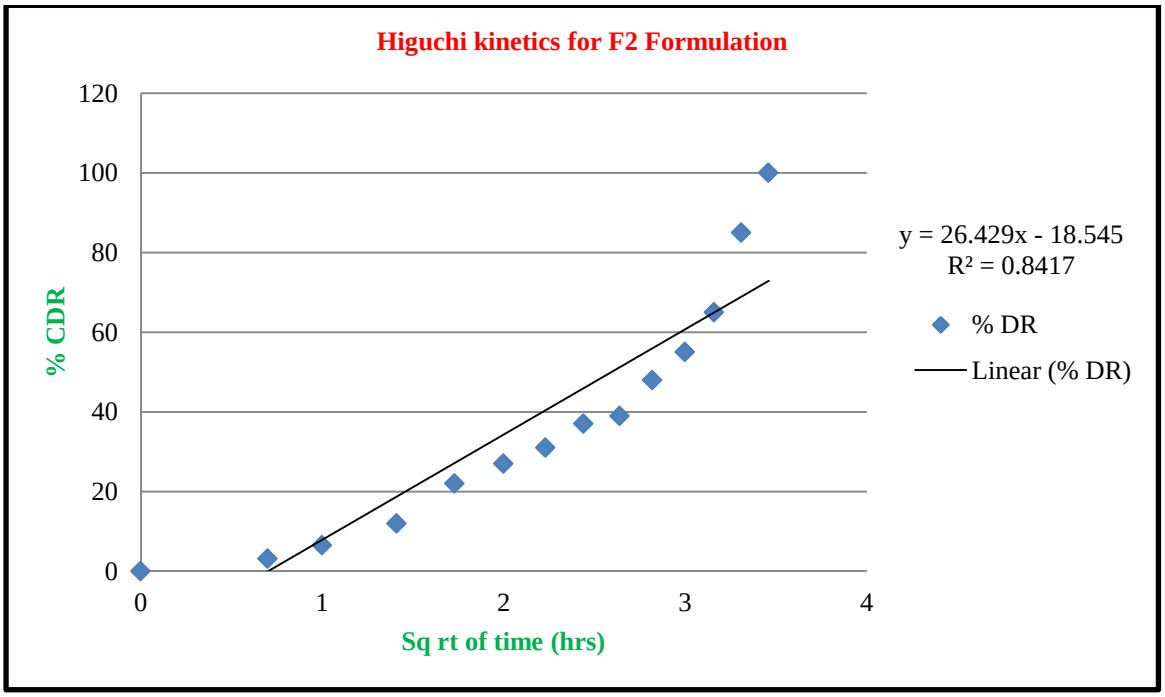

Fig 4: Higuchi graph for F2 Formulation

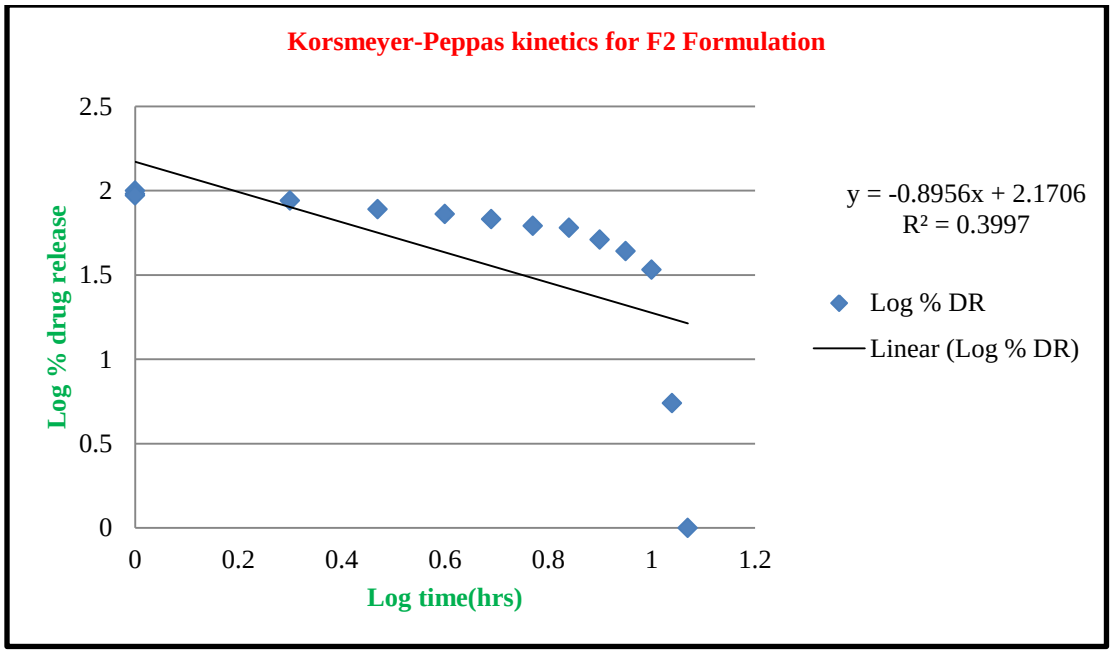

Fig 5: Korsmeyer-Peppas graph for F2 Formulation

Table 5: Release kinetics for F2 formulation for sustained release tablets

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	**Log % Remain Vs T**	**%CDR Vs √T**	**Log C Vs Log T**
Slope	7.353	0.108	26.42	0.895
R 2	0.952	0.601	0.841	0.399

Stability studies

Table 6: Stability studies of F2

Cumulative% drug release			
Sampling interval	**25^{0}C/60%RH**	**30^{0}C/65%RH**	**40^{0}C/75%RH**
0 Days	100.1	99.8	99.9
15 Days	98.5	98.6	98.2
30 Days	97.82	97.75	97.70
90 Days	96.45	97.32	97.26

Stability studies of the formulation F2 of Repaglinide (USP) matrix tablets were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25^o C/60%RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days. There was no significant change in the physical property and percent of drug release was within the limits ±4 during 8hour during the stability period.

DISCUSSION

The release profile of formulations F_1, F_2, F_3, F_4 F_5,F_6, F_7 and F_8 comprising various polymers like carrageenan, chitosan, bhara gum, gum karaya with varying concentrations. Formulations F_1, F_2, F_3, F_4 F_5,F_6, F_7 and F_8 exhibits release rates of 91%, 100% 94.2%, 91%, 97%, 89.8%, 83.6, 71.6% at various time intervals as shown in the table. Among all of these 8 formulations F_2 contains **carrageenan** shows maximum drug release at the end of 12hrs. Hence it

was optimized and decided to develop further formulations.

CONCLUSION

In this study matrix tablet of Repaglinide was prepared by wet granulation technique, using carrageenan, chitosan, bhara gum, gum karaya Polymers used as release retardant. It was found that increase in the concentration of excipients in polymeric ratio decreases the drug release. Carrageenan is non-carcinogenic, biocompatible and has high drug holding capacity. These led to its application as excipients in hydrophilic drug delivery system. The formulation F2 containing 30% carrageenan respectively showed good drug release with good matrix integrity. From the above result, it has been found that the optimized formula F2 containing 30% of carrageenan as drug retarding polymer shows better sustained effect for 12 hr when compared to other formulations. Different parameters like hardness, friability, weight variation, drug content uniformity, in-vitro drug release were evaluated for these formulations. Based on these results, formulation F2 was found to be the most promising formulations. The optimized formulation F8 follows zero order plot since the regression coefficient is 0.952 and plot was also found to be linear. The regression coefficient (R2) values of zero order in the optimized formulation F2 was greater than the R2 values of First order. Thus, the drug release follows zero order kinetics. The results suggest that the developed sustained release matrix tablets of Repaglinide could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus, the aim of this study was achieved.

REFERENCES

[1]. **Barot Nikunj, Darshan Modi**, "Formulation, Development and Evaluation Of Sustained Release Matrix Tablets Of Repaglinide". Nikunj Barot, 3(2), 2014, 370-396.

[2]. **Tapaswi Rani Dash, Pankaj Verma**, "Matrix Tablets: An Approach towards Oral Extended Release Drug Delivery". International Journal of Pharma Research & Review, 2(2), 2013, 12-24.

[3]. **Krushnakumar J Gandhi***, Subhash V Deshmane, "Polymers In Pharmaceutical Drug Delivery System: A Review". Int. J. Pharm. Sci. Rev. Res., 14(2), 2012, N° 10, 57-66.

[4]. **Jitender Joshi, Lata Bhakuni**, "Formulation and Evaluation of Solid Matrix Tablets Of Repaglinide", ISSN: 0976-8688; Der Pharmacia Sinica, 3(5), 2012, 598-603.

[5]. **Prakash Pavan, Porwal Mayor**, "Role of Natural Polymers In Sustained Release Drug Delivery System"ISSN 2230 – 8407(2), 2011, 9, 6 – 11.

[6]. **Balaji Venkataramanappa Kadri**, "Mechanism Of Drug Release From Matrix Tablets Involving Moving Boundaries" Department Of Pharmaceutical Sciences University Of Toronto; Master Of Science, 2001.

[7]. **Jaimini Manish***, Kothari Abhay, "Sustained Release Matrix Type Drug Delivery System: A Review", Journal Of Drug Delivery & Therapeutics; 2(6), 2012, 142-148.

[8]. **Baravaliya Smitaben** H., Tandel Jyotika G. "Analytical Method Development Of Repaglinide Formulation", Mohite Mukesh T et al/ IJRAP (4) 1, 2013.

[9]. **Gamal M El Maghraby1**, Mohamed A Osman, "Self Emulsifying Liquisolid Tablets For Enhanced Oral Bioavailability Of Repaglinide: In Vitro And In Vivo Evaluation", Journal Of Applied Pharmaceutical Science 4 (09), 2014, 012-021.

[10]. **Srinivas Mutalik, Krishnan Manoj**, "Chitosan And Enteric Polymer Based Once Daily Sustained Release Tablets Of Aceclofenac" AAPS Pharmscitech. 9(2), 2008, 651–659.

[11]. **Saptarshi D, Gupta MS**. "Modified release dosage form and drug delivery". Journal of Pharmacy Research. 2(11), 2009, 1728-29.

[12]. **Ansel HC, Allen LV**, **Popovich NC**. "Pharmaceutical dosage forms and drug delivery systems". Lippincott Williams and Wilkins; Baltimore 7, 2000, .231-75.

[13]. **James S and James C**, "Boylan encyclopedia of Pharmaceutical technology", 4th ed. Marcel Dekker; 1997, 304-07.

[14]. **Thomas WY, Joseph L**,"Sustained and Controlled release drug delivery system", Marcel Dekker; (6), 1978, 132- 34.

[15]. **Luana Periloli, Valeria Ambrogi. Et al**. "Mucoadhesive Bilayered Tablets for Buccal Sustained Release of Flurbiprofen". AAPS Pharm. Sci. Tech. 8(3), 2007, 54.

[16]. **Juan Manuel Llabot, Ruben Hilario Manzo. Et al**. "Double-Layered Mucoadhesive Tablets Containing Nystatin". AAPS Pharm. Sci. Tech. 3(3), 2002, 22.

[17]. **Narendra. Et.al.** "Optimization of Bilayer Floating Tablet Containing Metoprolol Tartrate as a Model Drug for Gastric Retention". AAPS Pharm. Sci. Tech. 7(2), 2006, 34.

[18]. **Vishnu M. Patel, Bhupendra G. Et al**., "Mucoadhesive Bilayer Tablets of Propranolol Hydrochloride". AAPS Pharm. Sci. Tech. 8(3), 2007, 77

[19]. **Chinam Niranjan Patra, Arethi Bharani Kumar. Et al**. "Design and evaluation of sustained release bilayer tablets of Propranolol hydrochloride". Acta Pharmaceutica., 57, 2007, 479-489.

[20]. **Girish S. Sonara, Devendra K. Jaina. Et al**. "Preparation and *in -vitro* evaluation of bilayer and floating-bioadhesive tablets of Rosiglitazone maleate". Asian Journal of Pharmaceutical Science. 2(4), 2007, 161-169.

[21]. **S Multak, A. Naha. Et al**."Preparation, *in-vitro,* Preclinical and Clinical Evaluations of Once Daily Sustained Release Tablets of Aceclofenac". Arch Pharm Res., 30(2), 2007, 222-234.

[22]. **A. B. Rathnanad. Et al.** "Design and Evaluation of Sustained release matrix tablet of Terbutaline Sulphate". Indian drugs. 44(3), 2007, 223-235.

[23]. **Dhake A. S. Et al**. "Formulation and Evaluation of Sustained release of Ofloxacin tablet". Indian drugs. 42(5), 2005, 317-318.

[24]. **Hiremath S. N. Et al**. "Formulation and Evaluation of sustained release matrix tablet of Metformin HCl". Indian drugs. 44(1), 2007, 52-53.

[25]. **Reddy K. R. Et al.** "Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and *In-vitro* Evaluation". AAPS Pharmaceutical Science Technology. 4(4), Article 61, 2003, 1-8.

[26]. **P.M. Dandagi. Et al**. "Preparation and evaluation of Theophylline and Salbutamol Sulphate matrix tablet". Indian Journal of Pharmaceutical Sciences. 67(9), 2005, 598-602.

[27]. **Pandey H. Et al.** "Preparation and evaluation of sustained release bilayer tablet of Domperidone". Indian drugs. 42(2), 2005, 84-86.

[28]. **Shirwaikar A. Et al**. "Sustained release bi-layered tablets of Diltiazem hydrochloride using insoluble matrix system". Indian Journal of Pharmaceutical Sciences. 66(4), 2004, 433-437.

[29]. **Hajare A. A. Et al**. "Formulation and release characteristics of sustained release Diltiazem hydrochloride tablets". Indian Journal of Pharmaceutical Sciences. 65(1), 2003, 44-48.

[30]. **Thilek kumar M. Et al.** "Preparation of HPMC based matrix tablet of Atenolol and cisapride and its evaluation". Indian Journal of Pharmaceutical Sciences. 67(4), 2005, 414-421.

[31]. **M A Abraham. Et al**. "Formulation and Evaluation of Bilayered concept of Sustained release of Ephedrine HCl tablets". Indian drugs. 44(6), 2007, 312-315.

[32]. **M Rani. Et al.** "Fabrication and Evaluation of Sustained release tablets of Diclofenac Sodium tablets". Indian Journal of Pharmaceutical Sciences. 63(3), 2001, 247-250.

[33]. **S. C. Basak Et al**. "Controlled release HPMC matrix tablets of Propronalol hydrochloride". Indian Journal Pharmaceutical Sciences. 66(6), 2004, 827-830.

[34]. **C Chebali. Et al.** "Effect of substituted amylase as a matrix for sustained release". International Journal of Pharmaceutics. 193, 2000, 167-173.

[35]. **M A Solinis**. **Et al**. "Formulation and Evaluation of Sustained release of Ketoprofen enantiomers". International Journal of Pharmaceutics. 239(1-3), 2002, 61-68.

[36]. **Rogelio Espinza, Enrique Hong, Leopoldo villafuerle**, "Influence of admixed citric acid on the release profile of Pelaserin hydrochloride from HPMC matrix tablets". International Journal of Pharmaceutics. 201, 2000, 165-173.

[37]. **Azarmi. Et al**. "Thermal treating as a tool for sustained release of Indomethacin from Eudragit RS and RL matrices". International Journal of Pharmaceutics. 246(1-2), 2002, 171-177.

[38]. **Koichiro Tahara. Et al**. "Application of model-independent and model analysis for the investigation of effect of drug solubility on its release rate from hydroxypropyl methylcellulose sustained release tablets". International Journal of Pharmaceutics. 133(1-2), 1996, 17-27.

[39]. **M. V. Velasco, A. Munog**. "*In-vitro* evaluation of sustained release matrix tablets prepared with new modified polymeric carbohydrates". International Journal of Pharmaceutics. 136, 1996, 107-115.

[40]. **Aleksandra Krajacic**. "Matrix formation in sustained release tablets with possible mechanism of dose dumping". International Journal of Pharmaceutics. 251, 2003, 67-78.