ejpmr, 2020,7(9), 291-298

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND CHARACTERIZATION OF SUSTAINED RELEASE MATRIX TABLETS OF AN ANTI DIABETIC DRUG

Medisetty Gayatri Devi[1], Lakshmi Usha Ayalasomayajula[2*], Radha Rani Earle[3] and Dr. P. Uma Devi[4]

[1,4]Department of Pharmaceutics, Viswandha Institute of Pharmaceutical Sciences, Sontyam, Visakhapatnam
[2,3]Department of Pharmaceutics, Maharajah's College of Pharmacy, Vizianagaram, A.P., India.

***Corresponding Author: Lakshmi Usha Ayalasomayajula**

Department of Pharmaceutics, Maharajah's College of Pharmacy, Vizianagaram, A.P., India.

Article Received on 11/06/2020 **Article Revised on 01/07/2020** **Article Accepted on 22/08/2020**

ABSTRACT

Diabetes Mellitus is a result of reduced insulin secretion from pancreas, and insulin action in the body or both. They are several natural as well as synthetic drugs like insulin, biguanides, sulphonylureas, thiazolidinodiones, meglitinides etc. for the treatment of diabetes. Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that enhances incretin hormone activity, sustains insulin levels, and reduces glycemia in Type II diabetes mellitus. Therefore it is an anti-diadetic drug used in the treatment of Type II diabetes mellitus and has been selected to prepare sustained release dosage forms. In present investigation an attempt has been made to design and develop Vildagliptin sustained release matrix tablets using Xanthan gum, Guar gum and their combination as release retarding polymers by direct compression method. Xanthan gum, Guar gum and their combination are used in various concentrations in the preparation of tablets. Hence sustained-release tablets were evaluated for various physical parameters namely– Hardness, Weight variation, Friability, Drug Content uniformity test etc. Drug release studies were also carried out in pH 6.8 phosphate buffer. By evaluating all the physical parameters and drug release studies F11 containing a mixture of Xanthan gum and Guar gum as release retarding polymer was optimized as the best formulation.

KEYWORDS: Diabetes Mellitus, Sustained release matrix tablets, Direct compression method, Xanthan gum, Guar gum.

INTRODUCTION

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Among the various drug delivery routes, the oral drug delivery has gained more attention due to its unique advantages like ease of administration, feasibility for solid formulations, patient compliance and an intensified immune response as in the case of vaccines. In addition, to these a large surface area of GIT (>300 m^2) lined with a viscous mucosal layer paves the way for drug attachment and subsequent absorption. Moreover in the GIT, drug molecules trapped within mucus are protected against the shear stresses caused by flowing gastric juices.[1]

A number of terms have been used to describe the oral dosage forms that represent modified release properties; which include delayed release, repeated action, prolonged release, sustained release, extended release and controlled release. Each drug delivery system is focused at eliminating the cyclical changes in plasma drug concentration seen after administration of conventional delivery systems. Modified release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant at a value within the therapeutic range of a drug for a significant period of time or achievement of a plasma concentration of a drug that delivers at a slow rate (i.e. sustained release) that stays within the therapeutic range for a longer period of time.[2] Sustained release, sustained action, prolong action, controlled release, extended action, depot are terms used to identify drug delivery systems that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Hypothetically, a sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion.[3]

Diabetes Mellitus is a chronic metabolic disorder due to impaired metabolism of carbohydrates, fats and proteins, characterized by hyperglycemia resulting from decreased utilization of carbohydrates and excessive glycogenolysis and gluconeogenesis from aminoacids and fatty acids. Diabetes may be identified by characteristic symptoms such as thirst, polyurea, blurring of vision and weight

loss. Diabetes Mellitus resulting from reduced insulin secretion from pancreas, and insulin action in the body or both. They are several natural as well as synthetic drugs like insulin, biguanides, sulphonylureas, thiazolidinodiones, meglitinides etc. for the treatment of diabetes.[4] Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that enhances incretin hormone activity, sustains insulin levels, and reduces glycemia in type 2 diabetes mellitus.

MATERIALS AND METHODS

Materials

The active ingredient Vildagliptin was received as a gift sample from Aurobindo Pharma Labs Ltd, Hyderabad. Xanthane gum, Guar gum, Microcrystalline cellulose, and Talc were received from Yarrow Chem Pvt.Ltd, Mumbai. All the other ingredients used in the formulation are of pharmaceutical analytical grade. Magnesium Steratre, Potassiun di hydrogen phosphate are obatained as gift samples from Oxford Pvt.Ltd and Sodium Hydroxide from Rankem Pvt Ltd.

Table No.1: Composition of 250mg Vildagliptin tablet.

S.No.	Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	Vildagliptin	50	50	50	50	50	50	50	50	50	50	50	50
2.	Xanthane gum	10	15	20	25	--	--	--	--	5	7.5	10	12.5
3.	Guar gum	--	--	--	--	10	15	20	25	5	7.5	10	12.5
4.	Micro crystalline cellulose	180	175	170	165	180	175	170	165	180	175	170	165
5.	Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
6.	Talc	5	5	5	5	5	5	5	5	5	5	5	5

Method

Direct Compression Method

Vildagliptin sustained release tablets were formulated using direct compression method. The formulations are prepared using Xanthane gum and Guar as drug release retarding agents. Varied concentrations of each polymers were used in the preparation of the formulations. The drug and all other excipients were sifted through ≠ 40 sieves separately and mixed thoroughly. The above blend was lubricated with magnesium sterate and the lubricated blend was compressed by using 8mm standard round faced punch on a16 station rotary tablet punching machine.[5]

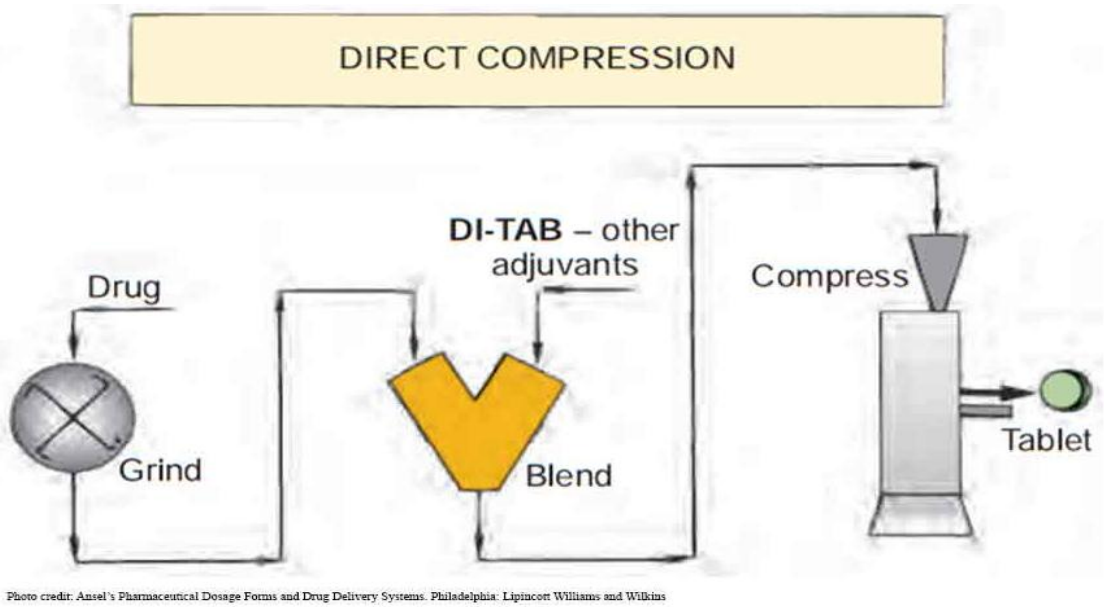

Fig 1: Diagrammatic representation of direct comprerssion method.

Evaluation parameters

Pre Compression Parameters

Prior to the compression of tablets, the blend of drug and excipients of all the batches were evaluated for various micromeritic properties like Angle of repose, bulk density, tapped density, Carr's Compressibility index and Hausner's ratio.

Post Compression Parameters

Thickness: Thickness of the sustained release tablets were tested using calibrated Vernier-calipers. The tablet thickness was controlled within a ±5% variation.

Hardness test or crushing strength: Hardness is the force required to break a tablet across the diameter. It is measured in kilograms and a crushing strength of usually

4kg is considered to be the minimum satisfactory for tablets. The hardness was tested using Monsanto hardness tester.[6]

Friability test: This is an in process quality control test performed to ensure the ability of tablets to withstand shocks during processing, handling, transportation, and shipment. It is usually measured by using Roche Friabilator.

$$\% \text{ Friability} = \frac{\text{Weight}_{\text{initial}} - \text{Weight}_{\text{final}}}{\text{Weight}_{\text{initial}}} \times 100$$

Uniformity of weight or Weight variation test: This test is performed to check the weight of the tablet frequently (every half an hour) so that in case of any corrections will be made during the compression of tablets. Any variation in the weight of the tablet may lead to over dose or under dose of medication. Therefore every tablet in each batch should have a uniform weight.[7]

% deviation= [(individual weight-average weight)] /average weight×100

Estimation of drug content: Drug content was determined accurately by weighing 5 tablets and crushing them in motor with the help of a pestle. Content uniformity was calculated using the following formula.

% purity =10 C (Au/As)

Where, C= Concentration, Au and As= absorbance obtained from the standard preparation and assay preparation respectively**.**

***In–vitro* drug release studies**

The dissolution behaviour of Domperidone was recorded using a dissolution apparatus (Disso 2000 LAB INDIA, Mumbai). USP dissolution apparatus with rotating paddle assembly (type II) was used at 50 rpm, in 900 ml of deionised water (phosphate buffer pH 6.8). The mean of the three determinations was used to calculate the drug release from the tablets. The samples were withdrawn at predetermined time intervals, and equal amount of fresh buffer was replaced. The obtained samples were filtered and assayed spectrophotometrically at 285nm.[8]

FT-IR Study

The FT-IR spectra of pure drug, polymers and optimised formulation were scanned over a frequency range 4000-400 cm-1 by placing sample on diamond ATR and analyzing for the presence of characteristic peaks.

RESULTS AND DISCUSSION

Precompression Parameters

Precompression studies are conducted in order to determine the flow-ability, compressibility studies of the powder blend and granules.

Different tablet batch formulations F1-F12 were prepared Solid dispersion mixture (75mg) and other all excipients were passed individually through #40 sieve and mixed well for 10 min in a mortar and pestle to form a powder blend. This blend was compressed into tablets by wet granulation and direct compression techniques using single punch rotary tablet punching machine using 8mm flat punches.[9]

Table No: 2 Pre compression parameters evaluation data of formulations F1 to F12.

S. No.	Formulation Code	Angle of repose	Loose Bulk Density	Tapped Bulk Density	Compressibility index	Hauser's ratio	Drug uniformity (%)
1.	**F1**	25.46± 0.447	0.4150±0.004	0.4832±0 .006	14.107± 0.908	1.164± 0.012	98.94±0.401
2.	**F2**	24.69± 0.447	0.4099± 0.003	0.4808± 0.006	14.753± 0.889	1.173± 0.012	97.31±0.438
3.	**F3**	27.14± 0.547	0.4049± 0.004	0.4695± 0.006	13.763± 0.861	1.160± 0.011	99.75±0.330
4.	**F4**	28.07± 0.547	0.4033± 0.004	0.4740± 0.009	14..922± 0.745	1.176± 0.016	98.31±0.410
5.	**F5**	27.39± 0.707	0.4001± 0.005	0.4695± 0.006	14.794± 0.971	1.174± 0.013	98.69±0.225
6.	**F6**	28.74± 0.557	0.3969± 0.004	0.4652±0.007	14..682± 1.071	1.172± 0.015	99.75±0.354
7.	**F7**	29.12±0.380	0.4021±0.002	0.4754±0.008	15.418±0.885	1.182±0.013	99.45±0.214
8.	**F8**	28.54±0.163	0.4692±0.003	0.5478±0.005	14.348±0.632	1.675±0.016	98.94±0.258
9.	**F9**	26.55±0.125	0.4210±0.002	0.4894±0.009	13.976±0.934	1.162±0.013	99.75±0.346
10.	**F10**	27.37±0.584	0.3894±0.006	0.4542±0.008	14.266±0.852	1.166±0.015	98.62±0.382
11.	**F11**	25.18±0.462	0.4018±0.003	0.4696±0.008	14.437±0.564	1.168±0.012	98.15±0.418
12.	**F12**	27.14±0.352	0.4060±0.002	0.4720±0.006	13.983±0.738	1.162±0.015	99.48±0.260

* All values are expressed as mean ± S.D, n = 3

Table No 3: Post Compression parameters evaluation data of formulations F1 to F12.

S. No.	Formulation Code	Diameter (mm)	Thickness (mm)	Weight variation (mg)	Hardness (Kg/Cm^2)	Friability (%)	Drug content (%)
1.	**F1**	8.03±0.016	2.52±0.026	151±7.5	5.1±0.124	0.120	99.355±0.361
2.	**F2**	8.02±0.004	2.55±0.030	150±7.5	5.4±0.248	0.066	98.820±0.478
3.	**F3**	8.03±0.004	2.53±0.034	154±7.5	5.3±0.210	0.133	99.530±0.410
4.	**F4**	8.03±0.008	2.54±0.028	145±7	5.2±0.232	0.132	99.425±0.314
5.	**F5**	8.06±0.012	2.53±0.017	147±7.5	5.9±0.126	0.166	97.860±0.618
6.	**F6**	8.05±0.012	2.52±0.020	151±7.5	5.2±0.142	0.232	99.443±0.489
7.	**F7**	8.04±0.016	2.54±0.015	152±7.5	5.4±0.180	0.146	98.548±0.724
8.	**F8**	8.03±0.012	2.55±0.015	149±7.5	5.3±0.228	0.191	99.234±0.463
9.	**F9**	8.02±0.012	2.61±0.010	148±7.5	5.9±0.219	0.149	98.906±0.226
10.	**F10**	8.03±0.012	2.55±0.041	153±7.5	5.8±0.160	0.193	98.026±0.624
11.	**F11**	8.03±0.016	2.63±0.026	150±7.5	6.2±0.126	0.154	99.477±0.354
12.	**F12**	8.05±0.016	2.61±0.030	148±7.5	6.1±0.113	0.046	99.240±0.162

Table No 4: *In vitro* release profile of Formulations F1 to F12.

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	23.591±0.610	21.592±0.480	18.373±0.477	15.218±0.101	34.124±0.138	31.267±0.305	24.473±0.475	20.495±0.331	25.375±0.269	20.145±0.465	14.264±0.254	10..343±0.465
2	33.195±0.880	27.942±0.621	23.171±0.241	23.443±0.858	47.431±0.432	45.422±0.263	43.197±0.702	29.194±0.770	34.043±0.392	27.622±0.145	22.689±0.534	17.543±0.035
3	54.091±0.346	49.213±0.587	36.977±0.137	33.080±0.082	58.177±019	58.331±0.288	57.165±0.188	44.076±0.356	44.432±0.786	45.689±0.493	28.543±0.323	26.678±0.570
4	64.745±0.542	59.842±0.529	48.986±0.219	42.981±0.130	65.288±0.542	65.403±0.529	63.574±0.219	54.025±0.130	50.165±0.361	65.143±0.365	42.549±0.045	43.114±0.428
6	78.252±0.285	72.099±0.408	64.033±0.163	57.059±0.219	81.210±0.285	75.442±0.408	73.437±0.163	70.115±0.219	83.865±0.034	78.534±0.547	76.243±0.653	72.354±0.512
8	90.020±0.168	83.966±0.746	78.260±0.319	70.031±0.281	85.556±0.168	82.180±0.746	79.439±0.319	77.047±0.281	95.449±0.543	94.638±0.376	88.207±0.434	80.587±0.540
12		96.963±0.268	94.070±0.187	83.998±0.134		94.313±0.268	90.292±0.187	84.092±0.235			97.184±0.632	89.365±0.067

Table No: 5 Regression co-efficient (r^2) of different kinetic models and diffusion exponent (n) of Peppas model.

Formulations	Zero order release		First order release		Higuchi release		Korsmeyer-Peppas	
	r^2	K_0	r^2	K_0		r^2	K_0	r^2
F_1	0.9454	9.568	0.9888	-0.1262	F_1	0.9454	9.568	0.9888
F_2	0.9078	6.9266	0.9718	-0.1259	F_2	0.9078	6.9266	0.9718
F_3	0.9583	7.1956	0.9742	-0.1035	F_3	0.9583	7.1956	0.9742
F_4	0.9629	6.3951	0.9974	-0.0670	F_4	0.9629	6.3951	0.9974
F_5	0.9424	7.3304	0.9881	-0.0980	F_5	0.9424	7.3304	0.9881
F_6	0.8946	5.3361	0.9885	-0.0941	F_6	0.8946	5.3361	0.9885
F_7	0.8464	5.3672	0.9879	-0.0770	F_7	0.8464	5.3672	0.9879
F_8	0.8748	5.8972	0.9688	-0.0668	F_8	0.8748	5.8972	0.9688
F_9	0.9773	10.614	0.9194	-0.1750	F_9	0.9773	10.614	0.9194
F_{10}	0.9628	11.008	0.9454	-0.1641	F_{10}	0.9628	11.008	0.9454
F_{11}	0.9073	8.3683	0.9772	-0.1418	F_{11}	0.9073	8.3683	0.9772
F_{12}	0.8928	7.8849	0.9735	-0.0918	F_{12}	0.8928	7.8849	0.9735

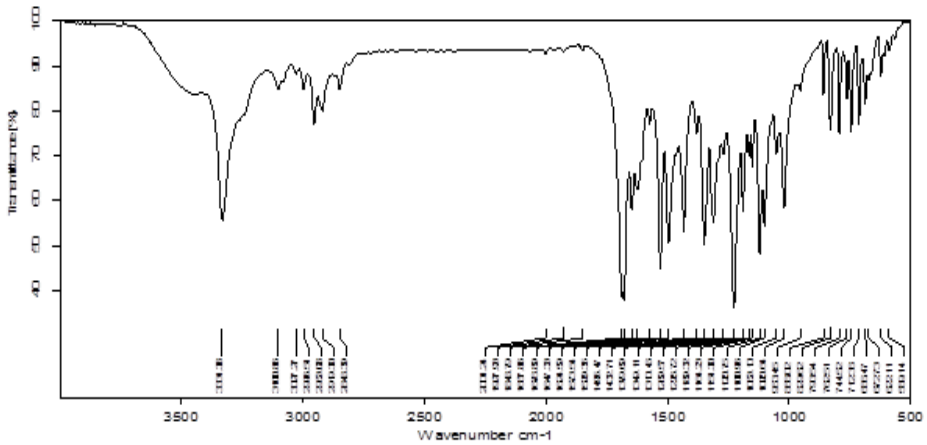

Fig No.2: IR Spectrum of Vildagliptin.

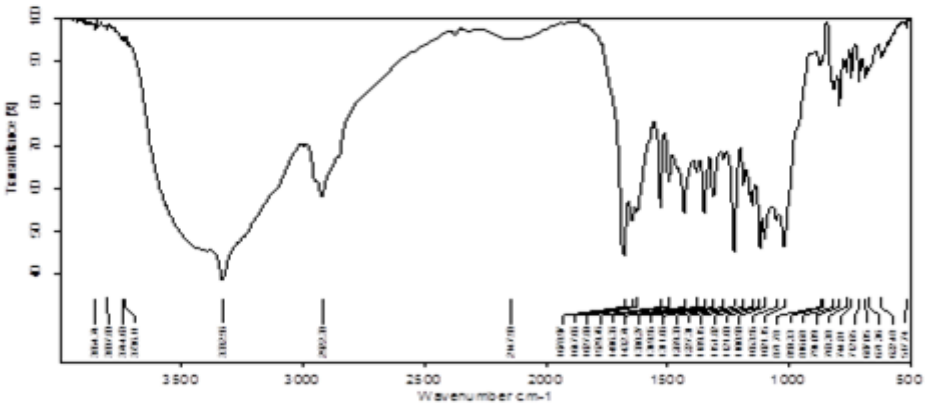

Fig No.3: IR Spectrum of Vildagliptin, Xanthan gum and Guar gum.

The blended granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density(TBD), compressibility index, Hauser's ratio and drug content uniformity. The results of these evaluations are as follows:-

Angle of repose: Angle of repose of the granules ranged from 24°69'± 0.447 to 29°12'±1.380. The results were found to be below 30^0 and hence the blend was found to have good flow property.

Bulk density and tapped density: Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.3894±0.006 to 0.4692±0.003 and 0.4542±0.008 to 0.4894±0.009 respectively.

Compressibility index (Carr's index): The compressibility index (%) ranged from 13.763± 0.861to 15.418 ± 1.145. The blend was found to have free flowing property as the result were found to be below 18%.

Hauser's Ratio
The Hauser ratio ranged from 1.160 ± 0.011to 1.182 ± 0.016. The result indicates the free flowing properties of the mixture blend.

Drug content uniformity: The drug content in a weighed amount of granules blend of all SR formulations ranged from 97.31±0.438 to 99.65±0.362.

Vildagliptin oral sustained-release tablets were evaluated for various physical parameters namely– Hardness, Weight variation, Friability, Drug Content uniformity test etc.

Diameter: The diameter of all batches ranged from 8.06±0.012 to 8.02±0.012 mm.

Thickness: The thickness of all batches ranged from 2.63±0.026 to 2.52±0.020 mm.
Hardness: The hardness of all batches ranged from 5.1-6.2 Kg/cm^2.

Friability: The percentage friability of all batches ranged from 0.046% to 0.232%.

Weight variation test: The percentage weight variations for all formulations are present in. All the formulations (F1-F12) passed weight variation test as per the Pharmacopoeias limits of 7.5%.

Drug content uniformity: Drug content was found to be uniform among the all formulations and ranged from 97.860 % to 99.477%.

***In-vitro* Dissolution Study**

The *in-vitro* drug release of the entire matrix tablets were carried in phosphate buffer pH 6.8 from 0 to 12 hrs by USP XXIV Type-II apparatus and the release data obtained from formulations were 90.020, 96.963, 94.070, 83.998, 85.556, 94.313, 90.292, 83.998, 95.449, 94.638, 97.184, 89.365 percent respectively.

By considering all the physical evaluation parameters and drug release studies F11 containing a mixture of Xanthan gum and Guar gum as release retarding polymer was optimized as the best formulation.

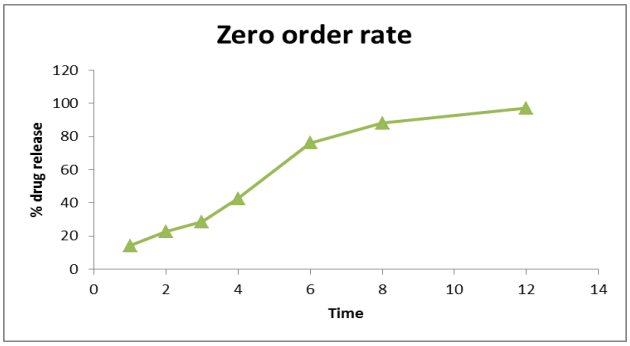

Fig No.4: Zero order release of formulation F11.

Fig No.5: First order release of formulation F11.

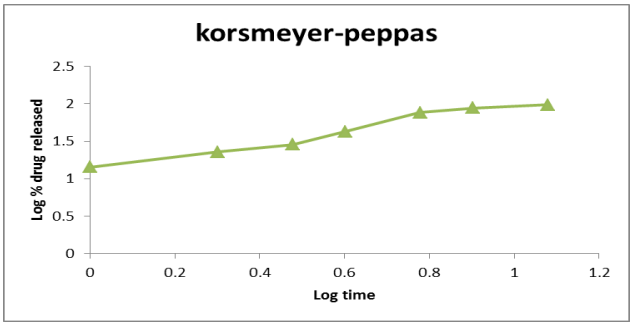

Fig.No.6: Korsmeyer-peppas kinetics of formulation F11.

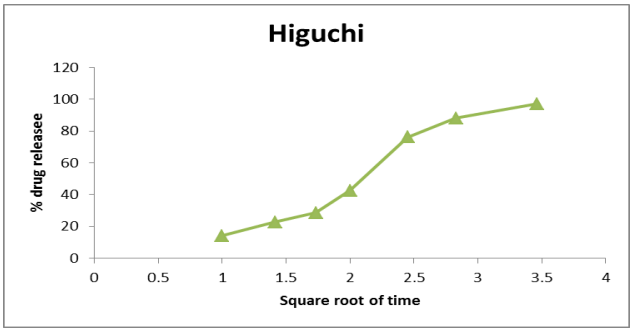

Fig No 7: Higuchi kinetics of formulation F11.

CONCLUSION

From the results it was observed that increasing the amount of polymer in the formulations, resulted in slower rate and decreased amount of drug release from the tablet. Comparison between Xanthan gum, Guar gum, and combination of Xanthan and Guar gum based tablets, release of drug from Guar gum based tablet was found to be faster compared to Xanthan gum and Xanthan and guar Gum combination based tablet. Order of retardation of different formulation is in the following sequence Xanthan guar combination > Xanthan gum > Guar gum.[10]

The maximum drug release was found to be 96.963±0.268% over a period of 12 hours in Xanthane gum based tablets (F2). Similarly maximum drug release was found to be 97.184±0.632% over a period of 12 hours in Xanthan gum & Guar gum combination based tablets (F11).

The formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to zero – order, first – order, Higuchi and peppas equations.[11] The data shows that, the release kinetics revealed that the formulations containing Xanthan gum follows first – order drug and Higuchi release with non-fickian diffusion, formulation containing Guar gum follows first – order drug release with fickian and non-fickian diffusion and the formulations containing Xanthan and Guar gum combination follows the zero, first and higuchi drug release with non-fickian diffusion.[12]

It can be concluded that Xanthan gum and Guar gum combination can be used as an effective matrix former to sustain the release of Vildagliptin for an extended period of 12 hrs as per USP dissolution requirements for Vildagliptin SR tablets.

REFERENCES

1. R.Panchagnula, singh and Y.Ashok Raj. Invitro evaluation of modified relese formulations of nifedipine from Indian market. Indian J Pharm Sci, 2007; 69(4): 556-561.
2. K.P.R. Chowdary and G.V. Radha. Synthesis, characterization and evaluation of starch acetate as

rate controlling matrix former for controlled release of nifedipine. *Int. J. Chem. Sci, 2011; 9(2): 449-456.*

3. Dewan T Akhter, Riaz Uddin, Naz H Huda and Kumar B Sutradhar. Design And Formulation Of Twice Daily Nifedipine Sustained Release Tablet Using Methocel K15m Cr and Methocel k100lv Cr. IJPPS, 2012; 4(1).
4. Donga JJ, Surani VS, Chauhan SP, Aundhia CJ, Seth AK. Formulation and in-vitro evalution of sustained release tablet of nifidipine using hydrophilic polymer. pharmasm.com, online published, 2011.
5. Prabakaran L,and Vishalini M . Hydrophilic polymers matrix systems of Nifedipine sustained release matrix tablets: Formulation optimization by Response Surface Method (Box-Behnken technique). Pelagia Research Library, Der Pharmacia Sinica, 2010; 1(1): 147-165.
6. Quiroga A., Bigatti G, Molinari M. Rajabi-Siahboomi A. development of a direct compression robust hydrophilic matrix of an insoluble micronized active using nifedipine as a model drug. Colorcon, Fraga 1039 1427 CABA.
7. Ramana G, Jyothirmai D and Sri Vaishnavi P. Sustain release of nifedipine from matrix ablets of its solid dispersion employing superdisinttegrants, IRJP, 2011; 2(9); 166-169.
8. KPR Chodwary, P Mohapatra, MN Murali Krishna. Evaluation of Olibanum resin as microencapsulating agent for controlled drug delivery. IJPS, 2006; 68(4): 461-464.
9. Lakshmi ushaAyalasomayajula, Radha Rani.E, M. Nishitha, K. Mounika, D. Anil Characterisation and comparison of drug release from gliclazide microcapsules prepared using natural and synthetic polymers. World journal of Pharmacy and Pharmaceutical Sciences, 2017; 6(9): 1465-1479.
10. Lakshmi usha Ayalasomayajula, Radha Rani.E, V.Swapna, Ch. Satyavathi Enhancement of solubility, preparation and evaluation of immediate release tablets of poorly soluble drug Repaglinide. Journal of Global Trends in Pharmaceutical Sciences, 2017; 8(3): 4130-4138.
11. Solmaz Dehghan1, Reza Aboofazeli, Mohammadreza Avadi and Ramin Khaksar. Formulation optimization of nifedipine containing microspheres using factorial design. African Journal of Pharmacy and Pharmacology, 2010; 4(6): pp. 346-354.
12. Radha Rani.E, Kiran Kumar Bandaru, Lakshmi usha Ayalasomayajula Formulation and characterization of sustained release coated matrix granules of Metformin Hydrochloride. Asian Journal of Pharmaceutical and Clinical Research, 2018; 11(7): 387-392.