An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

DESIGN AND CHARACTERISATION OF CONTROLLED RELEASE MATRIX TABLETS OF PIOGLITAZONE WITH NATURAL GUM

P.N. Mallikarjun*[a,b] , K.E.V. Nagoji[c] and Y. Srinivasa Rao[a]

[a.]Department of Pharmaceutics, Vignan institute of Pharmaceutical Technology, Duvvada, Visakhapatnam, Andhra Pradesh-530049, India

[b.]Acharya Nagarjuna University, Guntur, Andhra Pradesh-522010,India.

[c.]Sri Venkateswara college of Pharmacy, Etcherla, Srikakulam, Andhra Pradesh, India

***Corresponding author E-mail:** *mallik6567@gmail.com*

ARTICLE INFO

Key Words

Pioglitazone, *Avena sativa* , matrix tablets, PVP

ABSTRACT

The objective of this work was to develop and characterize controlled release matrix tablets of Pioglitazone an antidiabetic drug using gum derived from oats (*Avena sativa***)** as a release retardant agent. This gum extracted from oats by an established method. Fourier transform infrared spectroscopy studies were performed to find out the interactions between gum and drug. There was no significant interaction between drug and gum. Here matrix tablets of Pioglitazone were prepared with different ratios of gum alone and in combination with PVP by direct compression technique. Tablets thus formulated were evaluated for various quality control tests like weight variation, hardness, friability etc. All matrix tablets were found to have better uniformity of weight and drug content. After evaluation of physical characteristics of tablets, the *in vitro* dissolution test was performed in 0.1 N HCl up to 24 hours. The formulations PAMP3, PAMP4 and PAMP5 containing both gum and PVP controlled the release of drug up to 24 hours. The kinetic release data fitted into different mathematical models (Zero order, First order, Higuchi, Peppa's and Hixson-Crowell). Most of the solid matrix formulations followed Higuchi or zero order kinetics.

INTRODUCTION:

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration caused by insulin deficiency, often combined with insulin resistance. Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α. Pioglitazone is used for the treatment of diabetes mellitus type 2 in monotherapy and in combination with a sulfonylurea, metformin, or insulin. Pioglitazone has also been found to reduce the risk of conversion from prediabetes to diabetes mellitus type 2 by 72%. Pioglitazone also lowers the level of glucose in the blood by reducing the production and secretion of glucose into the blood by the liver[1]. Pioglitazone is an oral antidiabetic, belonging to the thiazolidinedione group of drugs. Pioglitazone commonly prescribing drug for patients with type II diabetes and it belongs to class II of Biopharmaceutical Classification System(BCS) having low water solubility which is rate limiting step in absorption of drug in Gastrointestinal tract [2]. Pioglitazone is

having short biological half life (3- 7 hrs) need to be administered more than once a day, which increases the possibility of non-compliance and produce greater fluctuations in plasma drug levels both above and below therapeutic range .[3] To reduce the frequency of administration and to improve patient compliance, controlled release formulation is desirable. The most commonly method of modulating the drug release is to include it in a matrix system. Because of their flexibility, desirable drug release profile, cost effectiveness and broad regulatory acceptance. Hence in the present work an attempt has been made to develop controlled release matrix tablets of Pioglitazone using natural gum and PVP[1]**.** Oats (*Avena sativa*) contains two major components, namely pentosan and β glucan. These are non starchy, gummy polysaccharides of cereal. β glucan ,which has been broadly established as a linear molecule composed of β-1,3- and β -1,4-linked D-glucopyranosyl units[4]. The Oats (*Avena sativa*) gum was utilized as release retardant agent in controlled release formulations[5]

MATERIALS AND METHODS:

Pioglitazone was obtained as a gift sample from the Dr.Reddy's labs, Hyderabad, India. The oats (*Avena sativa*) were purchased from local market of Visakhapatnam. Magnesium stearate and Talc were procured from Molychem, Mumbai. Micro crystalline cellulose, PVPK-30 purchased from Yarrow chem. Products, Mumbai.

Extraction of gum [4, 5, 6]

Water 500ml was added to 50g of oat flour, and the suspension was immediately adjusted to pH 10 with sodium carbonate (20%) and stirred vigorously for 0.5hr at 45^0C.The mixture was centrifuged in refrigerated centrifuge for 15 minutes (15000rpm). The cooled supernatant adjusted to pH 4.5 with 2M HCl and centrifuged for 30 minutes (15000rpm). The cooled supernatant made 50% with respect to IPA, which added slowly with vigorous stirring. The precipitate was allowed to settle overnight, collected by centrifugation. Washed with IPA, dried and powdered.

Drug-excipient compatibility studies[7, 8, 9]

Assessment of incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers were subjected to infra-red (IR) studies. The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2 mg sample in 200 mg KBr (Bruker FT IR). The scanning range was 400 to 4000 cm^{-1} and the resolution was $1cm^{-1}$. This spectral analysis was employed to check the compatibility of drugs with the excipients used.

Formulation of Pioglitazone Sustained Release Tablets by Direct Compression[9]: Controlled release matrix tablets of Pioglitazone with natural gum alone and along with PVP were prepared by using different drug and gum ratios as shown in Table 1.natural gum and PVP were used as matrix forming materials while MCC as direct compressible vehicle, Magnesium stearate as lubricant and Talc as glidant. All ingredients used were passed through a #100 sieve, weighed and mixed by geometric dilution technique to ensure uniform mixing. Later on the above blend is mixed for 5 min with sifted Magnesium stearate and talc for increasing the flow of blend. The prepared blend was subjected to direct compression using Elite eight station tablet making machine with 4-6 kg/cm^2 hardness of tablet.[10]

Evaluation of tablets:

(a) Physicochemical characterization of tablets: The prepared tablets were characterized for their physical characteristics like:

Hardness:

The Hardness of the prepared tablets was determined using a Monsanto Hardness tester. It is expressed in kg / cm^2.

Weight Variation:

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets less than 250 mg is 5.0%.

Friability: The Friability of the prepared tablets was determined using Roche friabilator. It is expressed in percentage. Ten tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4minutess. The tablets were dedusted and weighed (W_{final}). The % friability was then calculated by:-

$F= [(W_{initial}-W_{final})/ W_{initial}] X100$ (1)

Thickness: The thickness of twenty tablets of each formulation was measured by Vernier Calipers. It is expressed in mm.

Estimation of drug content in tablets:

Five tablets were accurately weighed and powdered. Tablets powder equivalent to 20 mg of the drug was taken for assay into 25 ml volumetric flask and 20 ml of methanol were added. The mixture was shaken thoroughly for about 30 min. to extract pioglitazone. The solution was then made upto volume with methanol. The methanolic solution was subsequently diluted suitably with 0.1N HCl and assayed at 269 nm for pioglitazone . Pioglitazone content of the tablets was calculated.

CSFR[11, 12]: The ratio of crushing strength-friability of tablets was determined as crushing strength-friability ratio

(b) *In vitro* characterization of tablets:

Drug release study on Pioglitazone Matrix Tablets:

Release of Pioglitazone from the matrix tablets prepared was studied in 0.1N hydrochloric acid (900 ml) using an eight station dissolution rate test apparatus (model, DS8000, M/s.Labindia) with a paddle stirrer at 50 rpm and 37 ± 0.5^0C. One tablet containing 30 mg of pioglitazone was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and were assayed at 269 nm for pioglitazone using Elico double beam UV/visible spectrophotometer .The sample (5 ml) taken at each sampling time was replaced with fresh dissolution medium (5 ml). The drug release experiments were conducted in triplicate.

Kinetics of *in vitro* drug release [13, 14, 15]

To study the release kinetics *in vitro* release data was applied to kinetic models such as zero-order, first order, Higuchi, Korsemeyer-Peppas and Hixson-Crowell equations.

Zero-order

$C = K_0.t$ (2)

Expressed in units of concentration/time, K o is zero order release constant and t is the time in hrs.

First-order

$\log C = \log C_0 – Kt /2.303$ (3)

Where C is the concentration, Co is the initial concentration of drug, K is the first-order rate constant, and t is the time

Higuchi

$Qt = K_H \cdot t^{1/2}$ (4)

Where Qt is the amount of release drug in time t, K_H is the kinetic constant and t is the time in hrs.

Korsmeyer and peppas

$M_t / M_\infty = K \cdot t^n$ (5)

Where M_t represents amount of the released drug at time t, M_∞ is the overall amount of the drug (Whole dose).

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickian diffusion. If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 0.5, then it is non- Fickian or anamolous diffusion and when n = 1.0 mechanism is non-Fickian case II diffusion, n > 1.0 mechanism is non- Fickian super case II.

Hixson and Crowell's cubic root law

$W_0^{1/3} – W^{1/3} = Kt$ (6)

W_0 is original mass of drug, W is remaining drug at time t and K dissolution rate constant

Model independent approaches[16, 17]

Dissolution efficiency ($DE_8\%$) up to 8 hours and mean dissolution time (MDT) were used to translate the profile differences into a single value

$$DE_8\% = \frac{\int_0^t y\,dt}{y_{100}}t \times 100 \quad (7)$$

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate. Where i is the dissolution sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and i-1, and ΔM is the amount of drug dissolved between i and i-1.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad (8)$$

RESULTS AND DISCUSSION

The quality control tests adopted for the prepared tablets are shown in the Table 2.The percent of weight variation for tablets passed weight variation test. The percentage weight variation was within the Pharmacopoeial limits of 5%. Tablet weight of all formulations varied from 197±0.6mg to 202±0.64mg and weight was found to be uniform. The thickness of the tablets ranged between 1.99±0.02 mm to 2.15±0.04mm.The drug content in all the formulations was within the range of 98.8%±1.25 to 102.5%±1.5.The hardness of the tablets ranged between 3.80±0.25kg/cm^2 to 4.50±0.5kg/cm^2.The percent friability of the prepared tablets was well within the acceptable limit. The results indicated that the tablets possessed enough mechanical strength to maintain integrity of the tablets. The crushing strength-friability ratio (CSFR) is a parameter used to evaluate the quality of tablets. The CSFR is a ratio of tablet strength (crushing strength) and weakness (friability). Higher CSFR values are indicative of tablets high quality .The CSFR values of all tablets range from 60.11 to 147.11.This indicated that tablets are of higher quality. The CSFR values are shown in Table 3. In FT-IR studies, Pioglitazone showed characteristic peaks at 2927.49.00 and 2926.76.81 cm^{-1} (3000-2850) (C-H); 1685.39 and 1685.00 cm^{-1} (1950-1600) (C=O); 1038.00 and 1037.80 cm^{-1} (1220-1020) (C-N) in alone and in formulation respectively. As there was no significant change in the spectra, it indicated that drug is compatible with natural gum. The FT-IR spectrums are shown in Figures 1 to 3.

***In vitro* drug release studies:**

Drug release profiles are shown in Figures 4 to 5.As the gum content increased in the formulations, percentage of drug released decreased. The formulations containing natural gum alone retarded the drug release up to 18hours at the maximum strength of 36 mg of gum in the formulation. This indicated that natural gum can retard the drug release successfully in all the formulations. The formulations containing natural gum and PVP retarded the drug release up to 24 hours. Release kinetics is an essential aspect of drug formulation development and kinetic data are also employed in setting *in vivo-in vitro* correlation of dosage forms. Pioglitazone release from the matrix tablets was studied in 0.1N hydrochloric acid. Pioglitazone release from all the matrix tablets prepared was slow and spread over 24 h and depended on the concentration of gum used and composition of the tablets. The drug release profile of all formulations are graphically represented in Figures 4-5.Table 4 present the kinetics of release of all formulations.

Table 1: Composition of matrix tablets of Pioglitazone using natural gum alone and With PVP

Formulation	PAM1	PAM2	PAM3	PAM4	PAM5	PAPM1	PAPM2	PAPM3	PAPM4	PAPM5
Pioglitazone	30	30	30	30	30	30	30	30	30	30
Avena sativa gum	6	12	18	24	30	6	12	18	24	12
PVPK-30	-	-	-	-	-	6	12	18	12	24
MCC	160	154	148	142	136	154	142	130	130	130
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2
Weight of tablet	200	200	200	200	200	200	200	200	200	200

Table 2: Evaluation parameters of prepared matrix tablets

Formulation	Uniformity of weight(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
PAM1	197±0.6	1.99±0.03	3.80±0.25	0.62±0.08	101.5±1.0
PAM2	199±0.56	2.1±0.03	4.20±0.5	0.58±0.09	102.5±1.25
PAM3	201±0.52	1.99±0.06	4.10±0.5	0.53±0.08	98.8±1.25
PAM4	201±0.60	2.07±0.02	4.10±0.25	0.51±0.07	99.9±1.0
PAM5	198±0.56	1.99±0.05	4.15±0.5	0.42±0.09	99.5±1.25
PAMP1	201±0.59	1.99±0.03	4.20±0.5	0.39±0.08	102.5±1.0
PAMP2	199±0.75	2.15±0.04	4.30±0.5	0.36±0.07	101.5±1.25
PAMP3	202±0.64	2.15±0.03	4.50±0.25	0.30±0.09	102.5±1.50
PAMP4	199±0.45	1.99±0.02	4.50±0.5	0.30±0.08	101.5±1.50
PAMP5	199±0.59	2.09±0.04	4.50±0.25	0.31±0.07	101.5±1.25

Table 3: CSFR values of tablets

Formulation	Crushing strength(N)	friability	CSFR
PAM1	37.27	0.62	60.11
PAM2	41.19	0.58	71.02
PAM3	40.21	0.50	80.42
PAM4	40.21	0.51	78.84
PAM5	40.70	0.42	96.90
PAMP1	41.19	0.39	105.61
PAMP2	42.17	0.36	117.14
PAMP3	44.13	0.30	147.11
PAMP4	44.13	0.30	147.11
PAMP5	44.13	0.31	142.36

Table 4: Correlation coefficient R^2 of all formulations

Formulation	Zero	First	Higuchi	Peppas	Hixson	n
PAM1	0.875	0.733	0.99	0.183	0.906	0.954
PAM2	0.888	0.725	0.993	0.294	0.96	0.933
PAM3	0.953	0.722	0.961	0.415	0.892	0.827
PAM4	0.953	0.859	0.986	0.529	0.967	0.827
PAM5	0.972	0.599	0.98	0.583	0.902	0.778
PAMP1	0.926	0.66	0.89	0.339	0.873	0.889
PAMP2	0.975	0.812	0.932	0.544	0.93	0.887
PAMP3	0.98	0.501	0.985	0.713	0.805	0.771
PAMP4	0.977	0.871	0.992	0.7	0.922	0.74
PAMP5	0.978	0.712	0.891	0.697	0.864	0.758

Table 5: MDT and DE_8% of all formulations

Formulation	DE%8	MDT(min)
PAM1	-	81.84
PAM2	-	106.59
PAM3	51.63	238.80
PAM4	44.73	307.80
PAM5	36.98	416.76
PAMP1	54.36	105.74
PAMP2	40.58	234.66
PAMP3	20.79	730.37
PAMP4	19.87	721.79
PAMP5	21.70	713.39

Figure 1: FT IR Spectrum of pure Pioglitazone

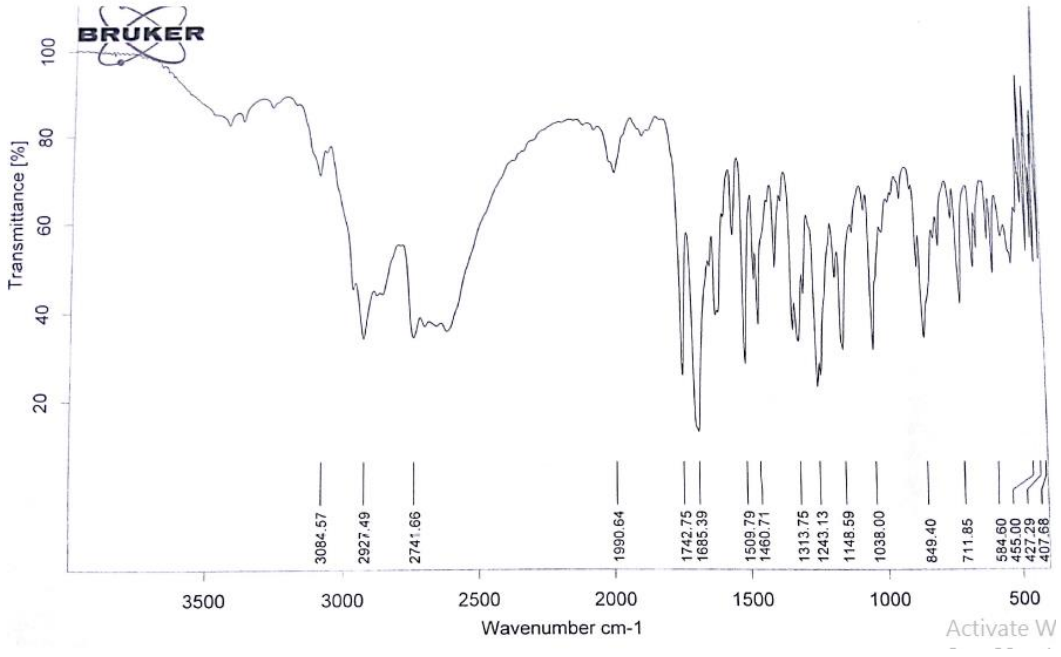


Figure 2: FT IR Spectrum of gum extracted from oats

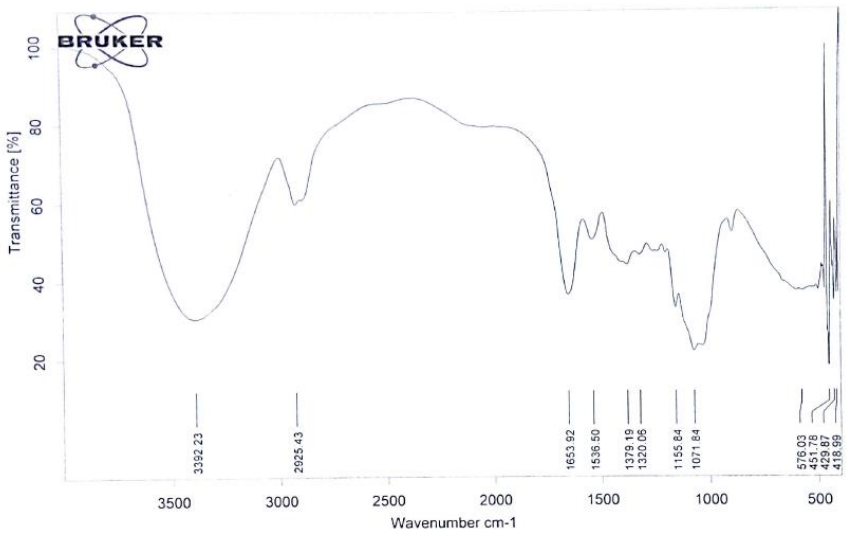


Figure 3: FT IR Spectrum of pioglitazone in formulation

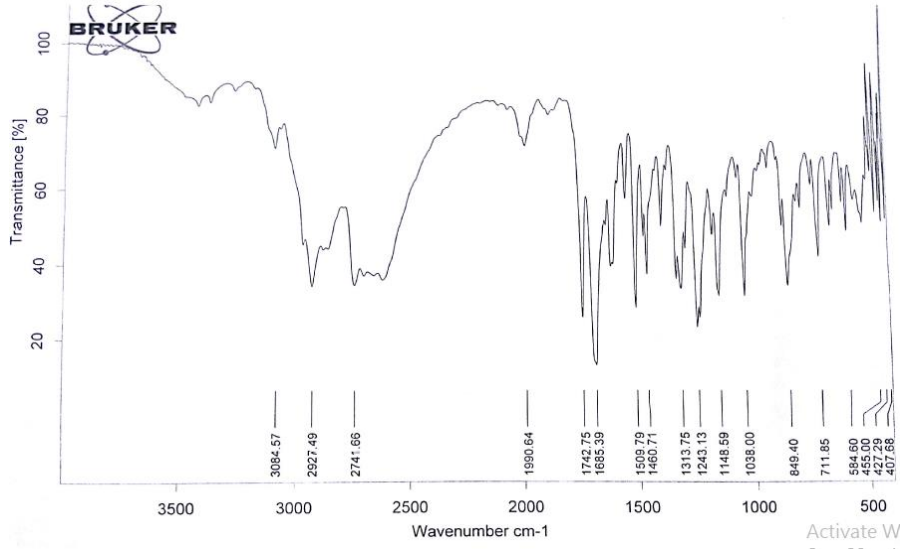


Figure 4: Drug release profiles of Pioglitazone from tablets containing natural gum alone

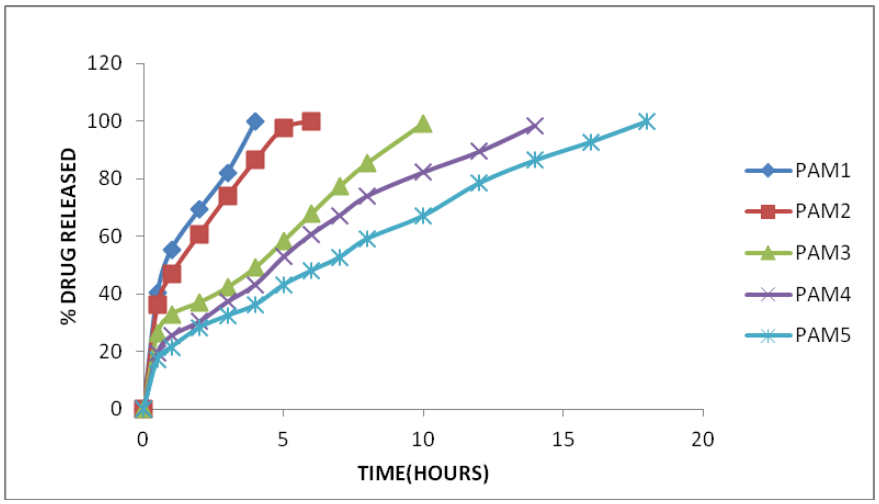
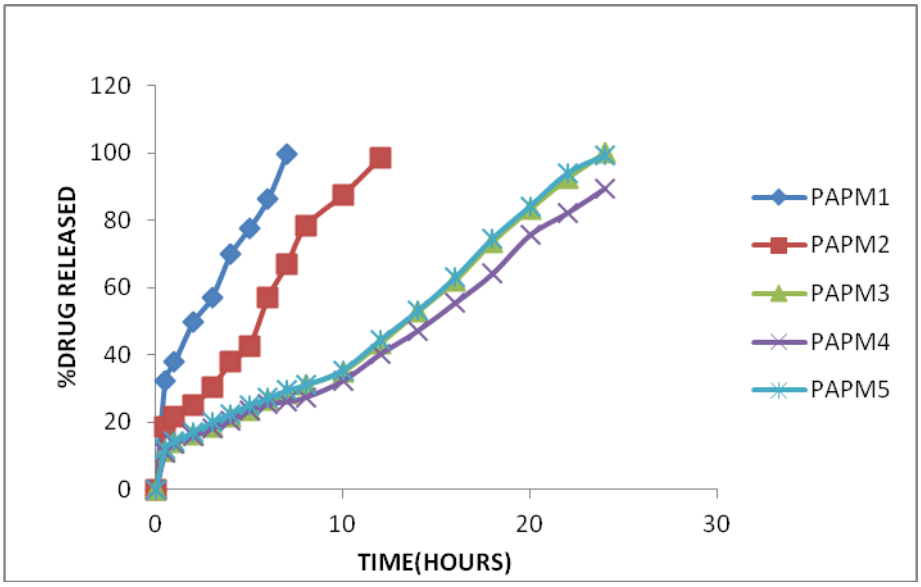


Figure 5: Drug release profiles of Pioglitazone from tablets containing natural gum and PVP



The kinetic model with the highest correlation coefficient value (R^2) was selected as the model that best described the dissolution data. Release data were analyzed by zero order, first order, Higuchi , Peppas and Hixson's crowell equation models. When the release data were analyzed as per zero and first order models, the R^2 values were relatively higher in zero order models with all the matrix tablets formulated indicating that the drug release from all these tablets followed zero order kinetics. When percent release was plotted against √time, linear regressions with R^2 > 0.89 were observed with all the matrix tablets prepared indicating that the drug release from all these tablets was diffusion controlled. When the release data were analyzed as per Peppas equation, the release exponent 'n' was found in the range 0.74 to 0.954 indicating Non-Fickian (anamalous) diffusion as the release mechanism from all the matrix tablets. All the formulations followed zero order release and Higuchi of release mechanism but none followed the Peppas model. The MDT and DE_8% are shown in Table 5. Comparing MDT and DE_8% of tablets showed that increasing MDT values as the concentration of gum increased. MDT values are PAM5> PAM4> PAM3 > PAM2 > PAM1for tablets with natural gum alone and PAMP3>PAMP4>PAMP5>PAMP2>PAM1 for tablets with natural gum and PVP.A reverse order of the effect was seen on the DE_8%. Greater the MDT relates to the greater capacity of retarding effect of the gum. The formulations PAMP3, PAMP4 and PAMP5 have Similar MDT and DE8% value with insignificant difference. This is may be due to total amount of gum and PVP in their formulations same (36mg).

CONCLUSION:

The compatibility between drug and gum was studied by using FTIR studies. The results depicted that drug and gum show no significant interaction between them. The evaluation results confirmed that the prepared tablets have exhibited satisfactory physicochemical properties such as weight uniformity, thickness uniformity, friability, hardness and drug content uniformity. These results assured that all physicochemical properties of tablets were within the acceptable limits. Release study of matrix tablets indicated the dug release from the formulations varies with different ratios of gum and PVP. Among all the formulations PAMP3, PAMP4 and PAMP5 are retarded the release of drug from tablet up to 24 hours. Based on the R^2 values it was confirmed that drug release followed Higuchi model and zero order release mechanism. According to the peppas diffusion exponent of release profiles the n values are above the 5 which indicates non-

Fickian diffusion. The objective of the present work was fulfilled that is formulation of controlled release matrix tablets of pioglitazone using natural gum. The natural gum alone efficiently controlled drug release up to 18 hours. Natural gum along with PVP gave slow, controlled and complete release of pioglitazone over 24 h apart from exhibiting good physicochemical characteristics. The present study revealed that natural gum appears to be suitable for use as a release retardant. Thus it was concluded that an effective controlled drug release system can be designed using natural gum derived from oats.

REFERENCES:

1. Sanjay Batra ,Mahesh kumar kataria and Ajay bilandi., A Review on Sustained Release Matrix Tablets of Pioglitazone. International Journal of Pharmaceutical Sciences Letters 2015, 5 (1), 509-511

2. Ram Chand Dhakar, Sheo Datta Maurya, Bhanu P S Sagar, Anish K Gupta, Ghanshyam Maurya, Development and evaluation of mucoadhesive microspheres of pioglitazone maleate, Journal of Pharmacy Research 2011,4(2),456-45.

3. Roathore M.S., Anil Middha, Gupta, V.B., Gaur, P.K., Tanaji Nandgude, In Vitro evaluation of ethyl cellulose microspears of pioglitazone, The Indian Pharmacist 2007 VI(63), 82-84

4. P.J. Wood, D. Paton, and I.R. Siddiqui. Determination of β- glucan in oats and barley: Cereal chem1976 54(3): 524-533.

5. P.N.Mallikarjun, K.E.V.Nagoji, Y.Srinivasa rao., Preparation and Evaluation Of Glipizide Oral controlled Release Matrix Tablets Using *Avena Sativa* Gum, World J pharmacy and pharma.sci. 2017 6(7),1156-1166

6. Wood, I.R. Siddiqui and D. Paton. Extraction of high viscosity gums from oats: Cereal chem1978 55(6), 1038-1049.

7. Subramaniam Kannan., Rangasamy Manivannan., Kugalur . Ganesan., Parthiban Kakkatummal Nishad., Natesan Senthil Kumar. Formulation and Evaluation of Sustained Release Tablets of Aceclofenac using Hydrophilic Matrix System. Int J PharmTech Res, 2010; 2(3): 1775-1780.

8. Bharadwaj TR, Kanwar M and LAl R. et al: Natural gums and modified gums as sustained release carriers. Drug Dev. Ind. Pharm. 2000; 26: 1025-1038.

9. Narasimha Reddy D., Srinath MS., Hindustan Abdul Ahad., Kishore Kumar Reddy B., Vamsi Krishna Reddy P., Krishna Mahesh Ch., Kranthi G., Raghavendra P. Formulation and in-vitro Evaluation of Glimepiride and Parecoxib Combination Mucoadhesive Tablets. Der Pharmacia Lettre. 2011; 3(1):185-192.

10. Venkatarajua MP, Godwaa DV, Rajesh KS and Shivakumara HG: xanthan and locust bean gum (from *Ceatonia siliquia)* matrix tablets for oral controlled delivery of propranolol hydrochloride. Asian Journal of Pharmaceutical Sciences 2007; 2 (6): 239-248.

11. Odeku, O.A.Assessmentof Albizia zygia gum as a binding agent in tablet formulations. Acta Pharm 2005; 55,263-276

12. Kwabena, Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. saudi Pharmacuetical journal 2016;24,82-91.

13. Londhe., Gattani., Surana. Development of floating drug delivery system with biphasic release for Verapamil hydrochloride: *Invitro* and *In-vivo* evaluation. J Pharm Sci and Tech. 2010; 2 (11): 361-367.

14. Varahala Setti ML., Vijaya Ratna J. Preparation and evaluation of controlled-release tablets of carvedilol. Asian J Pharm. 2009; 3: 252- 256.

15. Harris Shoaib M., Jaweria Tazeen., Hamid Merchant A, and Rabia Ismail Yousuf. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak J Pharm. Sci. 2006; 19 (2), 119-124.

16. Banakar UV. Pharmaceutical Dissolution Testing. New York, NY: Marcel Dekker Inc; 1992.

17. Gohel MC, Panchal MK. Novel use of similarity factors f2 and sd for the development of diltiazem HCl modified-release tablets using a 3^2 factorial design. Drug Dev Ind Pharm. 2002; 28: 77Y87.