Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Formulation Design and *In Vitro* Evaluation of Control Release Tablet of Pioglitazone HCl Solid Dispersion

SRUTI RANJAN MISHRA*[1], BHABANI SHANKAR NAYAK[1], SUPRAVA SETHY[1], P. ELLAIAH[1], GITANJALI MISHRA[2]

[1]Department of Pharmaceutics, Faculty in Pharmacy, Jeypore College of Pharmacy, Rondapalli, Jeypore – 764002, Koraput, Odisha, India.

[2]P.G. Department of Zoology, Berhampur University, Bhanja Bihar, Berhampur, Ganjam, Odisha, India

ARTICLE DETAILS

Article history:
Received on 19 February 2015
Modified on 15 April 2015
Accepted on 20 April 2015

Keywords:
Pioglitazone HCl,
β-cyclodextrin,
Kneading,
Antidiabetic,
Bioavailability,
Control release,
Tablet

ABSTRACT

The primary objective of the study is to enhance the bioavailability of pioglitazone HCl by kneading technique using pioglitazone HCl as drug and β-cyclodextrine as carrier in the ratios of 1:1, 1:2, 1:3 and 1:5 respectively. The prepared kneaded complexes were characterized for flow properties, drug content and *in vitro* drug release studies. The kneaded complex of pioglitazone is releasing 100 % drug within 45 min where as pure drug is releasing drug within 150 min. The kneaded complex formulation F1 of drug carrier ratio 1:1 was found to be best for excellent flow property, maximum drug content (88.76±0.23 %) and releasing maximum drug with least time. The drug excipient interaction study was carried out by Fourier Transform Infrared Spectroscopy (FTIR) and differential scanning colorimetric study. The solid dispersion formulation (F1) was used in preparation of control release tablet by direct compression method using hydroxyl propyl methyl cellulose (HPMC K4M) and ethyl cellulose as rate controlling polymers. The tablets were evaluated for thickness, diameter, weight variation, hardness, friability, *in vitro* drug dissolution and drug release kinetic studies. *In vitro* experiments indicated a sustained release over 11 h and acceptable tablet parameters as per USP-NF for formulation T9. Hence, it can be concluded that the formulation T9 containing HPMCK4M and ethyl cellulose (80 & 70 mg) has potential to deliver pioglitazone in a controlled and constant manner for prolong period over other formulations and can be adopted for a successful delivery of pioglitazone for oral use.

INTRODUCTION

Oral bioavailability of drugs depends on its dissolution rate, therefore major problems associated with these drugs was its very low aqueous solubility, which results into poor bioavailability after oral administration [1]. Solid dispersion prepared by kneading was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs [2, 3]. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone, β-cyclodextrin and polyethylene glycols are used as carriers for enhancement of aqueous solubility [4-6].

Author for Correspondence:
Email: sr.mishra69@yahoo.com

Pioglitazone hydrochloride is a thiazolidinedione antidiabetic agent that decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output [7]. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma [8]. The kneading complexes of pioglitazone solve the problems like gastro-intestinal disturbances, headache, dizziness, fatigue and insomnia [9]. The use of controlled release dosage forms offers numerous benefits including reducing gastro-intestinal disturbances, prolonging the release of drug hence decreasing frequency of dosing and decreasing side effects of drug by maintaining steady state concentration of drug in blood plasma [10]. The many design goals that need to be achieved in a successful controlled delivery system the two important are the achievement of

a sufficient input flux of drug and the achievement of a desired drug concentration-time profile [10].

MATERIALS AND METHOD

Pioglitazone HCl was obtained as gift sample from Cipla Ltd., Baddi, Himachal Pradesh, India. β-cyclodextrin, HPMCK4M, microcrystalline cellulose (MCC) (Avicel pH 101) and ethyl cellulose (ETHOCEL™ Standard 10 Premium EC STD 10) were procured from Loba Chemie Pvt. Ltd., Banglore, India. All other chemicals and reagents used were of analytical grade and procured from authorized dealer.

Preparation of Solid Dispersion by Kneading Technique

The kneading complexes were prepared using pioglitazone HCl as drug and β-cyclodextrine as carrier in the ratios of 1:1, 1:2, 1:3 and 1:5 (F1, F2, F3 and F4) respectively [3]. The pure drug of pioglitazone HCl was considered as formulation F0. The required quantity of carrier (β-cyclodextrin) was weighed in electronic digital balance (Sartorius Electronic balance, BT-2245, Calcutta, West Bangle, India), taken in a mortar and it was dissolved in methanol by using pestle. Accurately weighed quantity of drug was then added to methanol solution of carrier. The dispersion was then continuously stirred to form a paste was prepared. Above paste thus prepared was kneaded properly and kneaded complex was dried properly using Hot air oven (Rolex Pvt. Ltd., Calcutta, West Bangle, India) at 45°C for 1 h. The dried kneaded complex was passed through sieve no 80 and stored in a desiccator for further study.

Characterization of Pioglitazone Hcl Kneaded Complexes

Flow properties

Flowability of solid dispersions was investigated by determining angle of repose, bulk density, tapped density, Carr's index and Hausner ratio [11-13]. The angle of repose was determined by fixed funnel method. The kneaded complexes were tapped using bulk density apparatus (Excel Enterprises, Kolkata, West Bangle, India) for 100 taps in a cylinder and the change in volume were measured. Carr's index and Hausner ratio were calculated by the formula:

$$\textbf{Carr's index (\%)} = [(D_f - D_0) / D_f] \times 100$$

$$\textbf{Hausner ratio} = D_f / D_0$$

Where, D_f is tapped density; D_0 is poured density. All the experimental units were studied in triplicate (n=3).

Drug content

Solid dispersion (kneaded complex) equivalent to 25 mg of pioglitazone HCl was accurately weighed and it was dissolved in methanol. The solution was filtered through Whatmann filter paper no 1. The filtrate solution was suitably diluted with 0.1N HCl. Then the amount of drug present in solution was analyzed by using UV-Visible spectrophotometer (Shimadzu UV spectrophotometer, model 1700, Japan) at λ_{max} 269 nm [14]. All the experimental units were studied in triplicate (n=3).

In vitro Drug Release Study

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behavior. *In vitro* release profile for each solid dispersion (kneaded complex) as well as pure drug was performed using USP XXII type 2 dissolution apparatus (IP/ BP/ USP 8 paddle Digital Test Apparatus, Scientific Engineering Corporation Ltd., New Delhi, India) [15]. Sample equivalent to 30 mg of pioglitazone was added to 900 ml 0.1N HCl at (37±0.5)ºC and stirred at 50 rpm. An aliquot sample (5 ml) was withdrawn at an interval of 15 min with replacement of fresh medium and each drug solution was analyzed for pioglitazone content by UV-Visible spectrophotometer at 269 nm. The same method was adopted for each formulation of solid dispersion. All the experimental units were studied in triplicate (n=3).

Preparation of Control Release Tablet of Pioglitazone HCl

Various batches of pioglitazone HCl solid dispersion (Formulation F1 of drug carrier ratio 1:1) control release tablets (Nine formulations, T1 to T9) were prepared by direct compression method using excipients including HPMC K4M and ethyl cellulose in various proportions as mentioned in formulation design Table 2. Microcrystalline cellulose (MCC) (Avicel pH 101) was used in the formulation as diluents. Magnesium stearate was use as lubricant [16]. For all batches the solid dispersions were mixed with excipients in a Turbula apparatus (WA Bachofen, Basel, Switzerland) for 10 min at 30 rpm, and compressed between 7 mm round flat faced punches on a hand operated single punch tablet machine (Kilburn and co. ltd, kolkata).

Table 1: Flow Properties, Drug Content and *In Vitro* Drug Release Study of Various Pioglitazone Hcl Kneaded Complexes.

Parameters	F1	F2	F3	F4
Bulk density (g/cc) (X±S.D.)	0.93±0.33	0.82±0.13	0.81±0.42	0.80±0.31
Tapped density (g/cc) (X±S.D.)	1.01±0.22	0.98±0.18	0.97±0.31	0.95±0.45
Carr's Index (%)	7.920	16.326	16.992	16.970
Hausner's ratio	1.086	1.041	1.197	1.187
Angle of repose (°) (X±S.D.)	21.2±0.22	26.4±0.32	28.29±0.42	29.21±0.31
Flow comment	Excellent	Good	Good	Good
Drug content (%) (X±S.D.)	88.76±0.23	85.61±0.14	79.82±0.31	78.02±0.19
Cumulative % drug release (X±S.D.)	99.12±1.45	98.58±1.21	97.27±1.09	96.96±1.11

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	54.51705	3	18.17235	0.15486	0.049213	6.591382
Within Groups	469.3883	4	117.347075			
Total	523.9054	7				

Each value is expressed as mean ± standard deviation (n = 3). Standard error of mean < 0.837. Data are found to be significant (*F value < F crit*) by testing through one way ANOVA at 5 % level of significance (p < 0.05 that is p = 0.049213). ANOVA – Analysis of Variance, df – Degree of freedom, P – Probability, F – Anova value, SS – Square valu and MS – Mean square value.

Table 2: Formulation Design of Pioglitazone Controlled Release Tablets Using Hpmc K4m and Ethyl Cellulose.

Ingredients	Quantity of ingredient / Tablet (mg)								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pioglitazone	116	116	116	116	116	116	116	116	116
HPMC K4M	40	100	115	-	-	50	50	65	80
Ethyl cellulose	40	-	-	100	115	60	75	60	75
MCC	80	35	20	35	45	50	35	25	05
Mg stearate	4	4	4	4	4	4	4	4	4
Total weight	280	280	280	280	280	280	280	280	280
ANOVA	-	-	-		-		-	-	
Source of Variation	SS	df	MS		F		P-value	F crit	
Between Groups	234.4444	8	29.30556		0.011904		0.04854	2.208518	
Within Groups	88628	36	2461.889		-		-	-	
Total	88862.44	44	-		-		-	-	

Formulation is found to be significant (*F value < F crit*) by testing through one way ANOVA at 5 % level of significance (p < 0.05 that is p =0.04854). ANOVA – Analysis of Variance, df – Degree of freedom, P – Probability, F – Anova value, SS – Square valu and MS – Mean square value.

Drug Excipients Interaction Study

Fourier Transforms Infrared Radiation (FT-IR) Studies.

The FT-IR (Shimadzu IR spectrophotometer, model 840, Japan) was used for these IR analyses in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution [11]. The samples of pure drug pioglitazone, kneaded complex of drug-carrier and physical mixtures of pioglitazone HCl solid dispersions with HPMCK4M and ethyl cellulose were prepared separately by palletization technique in KBr using IR press. The IR peaks of pure pioglitazone were analyzed and were compared with the peaks obtained from kneaded complexes and tablet granules.

Differential Scanning Colorimetric (DSC) Study
DSC was performed on a Shimadzu DSC-60 (Shimadzu, Japan). A 1:1 ratio of drug and excipient was weighed into aluminum crucible and sample was analyzed by heating at a scanning rate of 100°C/min over a temperature range 200-3000°C under a nitrogen flow of 40ml/min [17]. Reproducibility was checked by running the sample in triplicate.

Quality Control Test on the Tablets

Thickness and Diameter
The study of the tablet thickness was conducted by the following USP guidelines (The USP-NF, 2002) [18]. For these fifteen tablets were taken for each batch and thickness were measured by using Digimatic caliper, Mitutoyo Corporation, Japan.

Weight Variation
Weight variation study was conducted by following guidelines of USP (USP-NF, 2002). In short 20 tablets were taken and they were weighed together and individually in electronically digital balance. The individual weight variations were studied from the mean weight of each set. Four such sets were run [18].

Hardness
Hardness study was conducted by following the guidelines of the USP-NF, 2002 [18]. Six tablets were taken and hardness of each tablet of each batch was measured by Monsanto type Hardness Tester (Campbell Electronics Company, Mumbai, India).

Friability
Friability testing (The USP-NF, 2002) was done by using 6 tablets for each batch by using Friability Test Apparatus (Campbell Electronics, Mumbai, India) [18].

Drug content
About 20 tablets were selected randomly from each formulation, weighed. The weighed tablets were powdered. The powder equivalent to 100 mg of pioglitazone was accurately weighed and dissolved in phosphate buffer pH 6.8. After suitable dilution, the solution was analyzed for drug content by using UV-Visible spectrophotometer (Shimadzu UV 1700, Japan) at 252 nm.

In vitro Dissolution Study
In vitro drug release study was carried out in USP XXI paddle type dissolution test apparatus (Electrolab TDT-08L, Mumbai, India) using simulated gastric fluid (0.1N HCl) as dissolution medium (900 ml of dissolution medium at 37±1°C was adjusted to 100 rpm) [18]. An aliquot sample (5 ml) was withdrawn at an interval of 1 h and filtered through Whatmann filter paper No.41. The withdrawn sample was replaced with fresh dissolution media and analyzed for Pioglitazone HCl content by UV-Visible spectrophotometer (Shimadzu UV 1700, Japan) at 269 nm. All the experimental units were evaluated in triplicate (n=3).The same method was adopted for each batch of tablet.

Drug Release Kinetic Study
In order to study the exact mechanism of drug release from the pioglitazone controlled release tablet, drug release data was analyzed according to zero order, first order, higuchi square root and Korsemayer-Peppas kinetic equation [19-21]. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Statistical Analysis
Each value is expressed as mean ± standard deviation (n = 6). For determining the statistical significance, standard error mean and one way analysis of variance (ANOVA) at 5 % level significance was employed. P values < 0.05 were considered significant [22-23].

RESULTS AND DISCUSSIONS
The bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index values of the prepared solid dispersion are represented in Table 1. The bulk density was found in the range of 0.80±0.31 to 0.93±0.33 g/cc. The solid dispersion of all formulations had Hausner's ratio of 1.197 or less indicating good flowability. The Carr's index was found between 7.920 to 16.992 %. The good flowability of the prepared kneaded complexes (solid dispersion) was also evidenced with angle of repose within range of 21.2±0.22 to 29.21±0.31°, which is below 30° indicating good flowability. The flowability of solid dispersion formulation F1 was found to be excellent as its Carr's index is 7.920 and angle of repose is 21.2±0.22°. Relatively high drug content was observed for each formulation as presented in Table 1. The drug content was found in the ranges of 78.02±0.19 to 88.76±0.23 %. The maximum drug content was obtained with formulation F1. The *in vitro* drug releases of acquired solid dispersions were shown in Table 1 and Fig 1.

Table 5: Cumulative % Drug Released From Various Formulations Using Hpmc K4m And Ethyl Cellulose

Sl. No.	Time (h)	Percentage cumulative drug release								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	0	0	0	0	0	0	0	0	0	0
2	0.5	0.69	1.31	1.01	1.01	2.4	1.16	1.93	0.54	0.85
3	1	5.6	6.42	5.49	10.28	12.14	6.26	7.96	4.17	3.32
4	2	12	18.63	18.02	19.72	18.79	16.31	18.32	13.69	10.9
5	3	18.32	19.84	18.68	23.26	20.35	17.69	20.24	15.25	11.03
6	4	24.20	22.12	21.86	29.49	28.92	22.31	26.12	18.43	21.2
7	5	30.97	27.27	26.48	42.01	46.29	36.99	32.59	22.51	25.1
8	6	46.9	33.33	33.43	59.74	71.03	58.31	64.82	28.2	32.23
9	7	65.35	48.72	44.54	86.09	98.46	86.1	94.04	40.18	40.04
10	8	89.01	69.15	59.73	-	-	-	-	54.14	50.14
11	9	-	99.45	77.82	-	-	-	-	70.25	57.8
12	10	-	-	99.32	-	-	-	-	87.45	73.9
13	11	-	-	-	-	-	-	-	-	97.5
ANOVA		-		-	-		-	-		-
Source of Variation		*SS*		*df*	*MS*		*F*	*P-value*		*F crit*
Between Groups		2680.264		8	335.033		0.383723	0.039201		2.033295
Within Groups		86438.06		99	873.1117		-	-		-
Total		89118.33		107	-		-	-		-

Datas are found to be significant (*F value* < *F crit*) by testing through one way ANOVA at 5 % level of significance ($p < 0.05$ that is0.039201). ANOVA – Analysis of Variance, df – Degree of freedom, P – Probability, F – Anova value, SS – Square valu and MS – Mean square value.

Table 6: *In vitro* Drug Release Kinetic Studies of Different Tablet Formulations

Formulations	Zero order kinetics	First order kinetics	Higuchi equation	Korsemeyer-Peppas	Release Exponent (n)
	Regression co-efficient (r^2)				
F1	0.924	0.7261	0.8349	0.972	1.28
F2	0.861	0.7967	0.7665	0.906	1.66
F3	0.909	0.786	0.8159	0.933	1.12
F4	0.927	0.750	0.856	0.937	1.015
F5	0.898	0.589	0.809	0.873	1.035
F6	0.887	0.714	0.797	0.925	1.235
F7	0.899	0.658	0.810	0.927	1.176
F8	0.913	0.740	0.816	0.942	1.164
F9	0.9602	0.801	0.847	0.933	1.29

r – Regression co-efficient.

The *in vitro* dissolution study revealed that the release rate was increased with decreased proportion of polymer that β-cyclodextrine. Cumulative percent drug released after 45 min was 99.12±1.45, 98.58±1.21 (60 min study), 97.27±1.09 and 96.96±1.11 % for F1, F2, F3 and F4 respectively and was 98.19±1.04 % in 150 min for pure drug (Fig 1). The result (As given in Table 1) reveled that with increase in concentration of carrier β-cyclodextrine, marked decrease in drug release was obtained. From the *in vitro* drug release profile, it can be seen that formulation F1 (1:1 ratio of drug: β-cyclodextrine) shows higher dissolution rate compared with other formulations. Thus solid dispersion formulation F1 containing pioglitazone and β-cyclodextrine in the ratio of 1:1, is the best optimized formulation for designing of controlled release tablet.

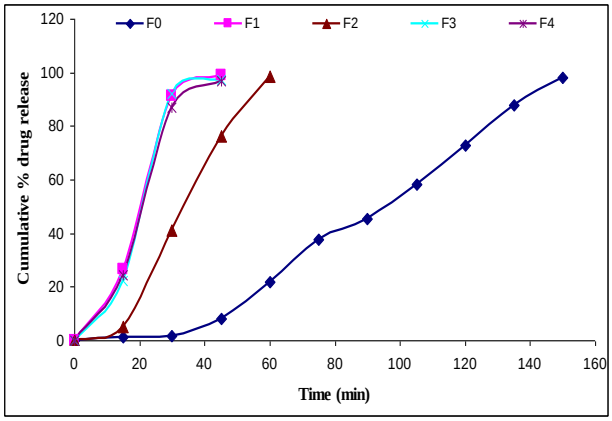
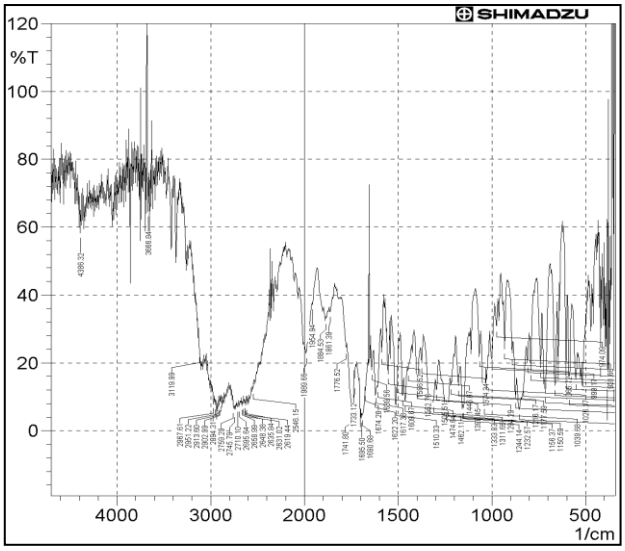
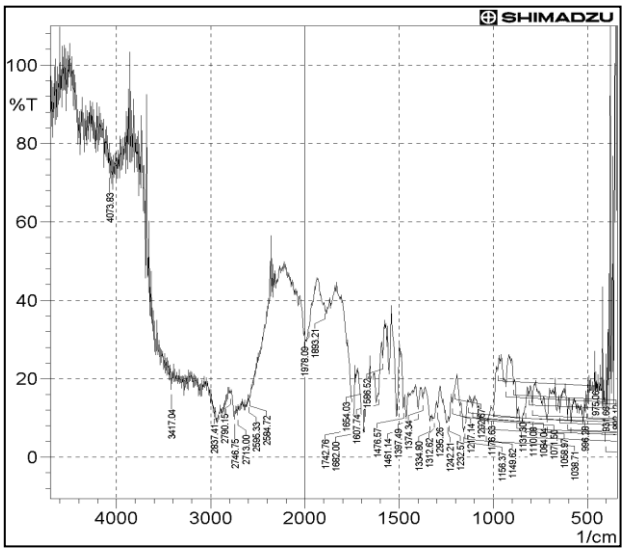


Figure 1: *In vitro* Drug Release Profile of Kneaded Pioglitazone Complex in 0.1n HCl.
F0 – Pioglitazone HCl Pure Drug.



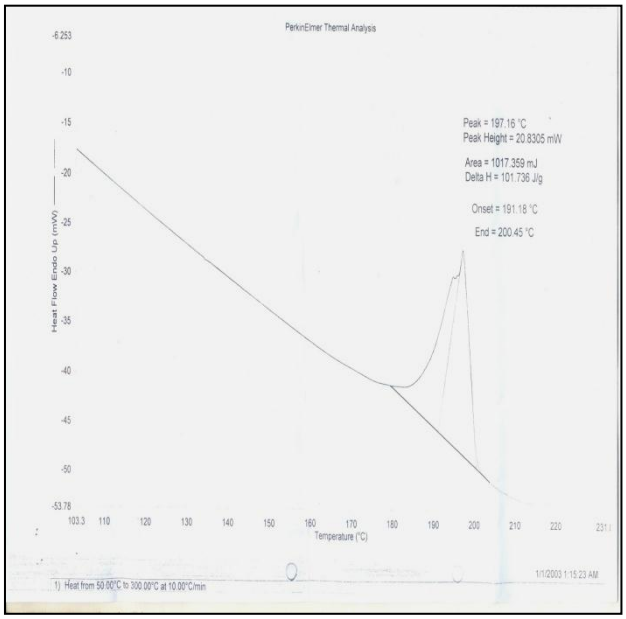
(A)



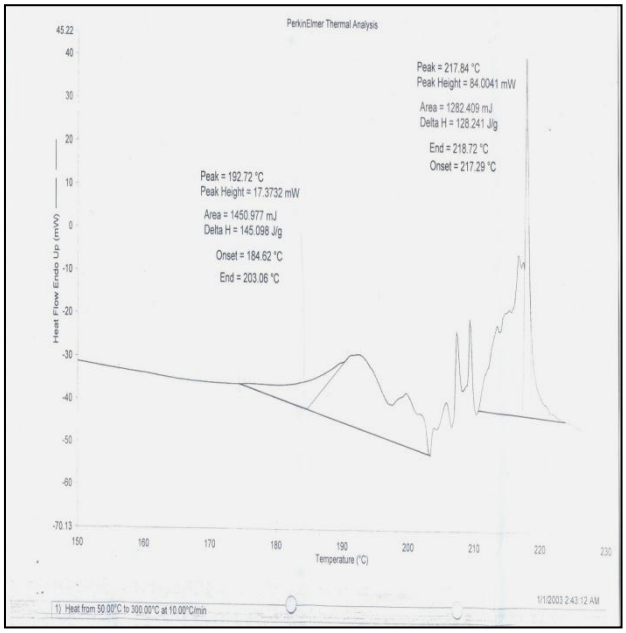
(B)

Figure 2: FTIR Spectra of Pure Drug Pioglitazone HCl and Pioglitazone β-cyclodextrine Kneaded Complex in the Frequency Range between 4000 and 600 cm^{-1} and at 1 cm^{-1} Resolution.

The interaction between the drug and the carrier often leads to identifiable changes in the FTIR profile of solid systems. FTIR spectra at 45 scans and a resolution of 1 cm-1 were recorded in KBr pellets for pure drug (Fig 2A) and the solid dispersion (kneaded complex) (Fig 2B) as represented in Fig 2. The spectrum of solid dispersion (kneaded complex) was equivalent to the addition spectrum of polymer and drug indicating no interaction occurring in the simple physical mixture of drug and polymer.



(A)



(B)

Figure 3: Differential Scanning Colorimetric Study of Pure Drug, Pioglitazone and Pioglitazone - β-cyclodextrin Inclusion Complex.

The results of differential scanning colorimetric study are shown in Fig 3 (A and B). The study revealed that there is no significant change in melting point of pioglitazone compared between peaks of pioglitazone and other pioglitazone β-cyclodextrine kneaded complex, signifying that no such significant interaction is taking place between pioglitazone and excipients. The diameter (7.93±0.05 to 7.98±0.051 cm) and thickness (2.2±0.45 to 2.8±0.41 cm) of all tablet formulations was almost same (Table 3). All the batches of tablets exhibited equal uniformity in weight (244.36±5.89 to 278.29±6.60 mg) as given in Table 3.

The hardness of all tablet formulations was ranged from 5.0±0.28 to 6.0±0.356 kg/cm^2 (Table 4). All tablet formulations passed hardness test as per Pharmacopoeial limits of USP-2002, as hardness must be within 5 to 6 kg/cm^2. The friability of all tablet formulations was ranged from 0.539±0.91 to 0.583±0.62 %. All tablet formulations passed friability test as per Pharmacopoeial limits of USP-2002, as percentage loss on friability was less than 1%, as represented in Table 4.

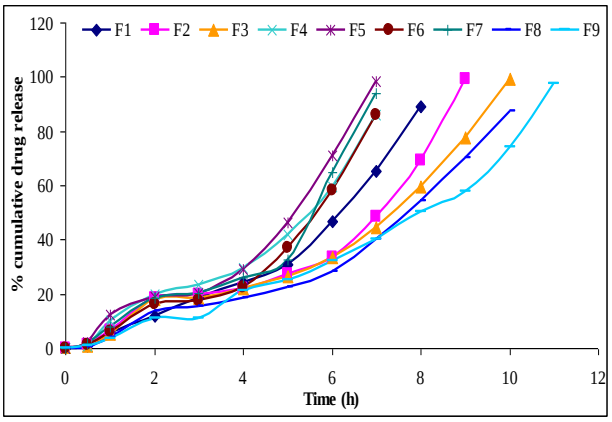


Figure 4: *In vitro* Drug Release Profile of Various Pioglitazone Controlled Release Tablet Formulations.

All the batches of tablets exhibited good uniformity in drug content (98.73±2.12 to100.04±2.27) as shown in Table 4. The maximum drug content (100.04±2.27 %) was achieved with tablet formulation F3 using HPMC K4M as rate controlling polymer only.

All most all pioglitazone controlled release tablet formulations were able to release drug in controlled manner over extended period of time (Data given in Table 5 and Fig 4).

Table 3: Diameter, Thickness and Average Weight Evaluation Data of Pioglitazone Hcl Controlled Release Tablet Formulations.

Formulations	Diameter (cm) (X±S.D.)	Thickness (cm) (X±S.D.)	Average weight (mg) (X±S.D.)
F1	7.94±0.053	2.3±0.86	246.23±6.21
F2	7.93±0.05	2.2±0.84	244.36±5.89
F3	7.98±0.044	2.5±0.61	259.51±6.11
F4	7.97±0.049	2.5±0.96	245.162±6.1
F5	7.98±0.051	2.6±0.77	259.48±6.15
F6	7.96±0.044	2.3±0.69	256.85±6.35
F7	7.95±0.047	2.8±0.41	268.63±6.41
F8	7.97±0.047	2.7±0.67	269.37±6.72
F9	7.96±0.049	2.2±0.45	278.29±6.60

Each value is represented as mean ± standard deviation (n = 3). Standard error of mean < 4.897

Table 4: Hardness, Friability, Drug Content and *In Vitro* Drug Release Data of Pioglitazone Hcl Controlled Release Tablet Formulations.

Formulations	Hardness (Kg/cm^2) (X±S.D.)	Friability (%) (X±S.D.)	Drug Content (%) (X±S.D.)
F1	5.5±0.324	0.553±0.34	99.314±2.02
F2	6.0±0.356	0.542±0.22	99.64±2.055
F3	5.0±0.405	0.573±0.87	100.04±2.27
F4	5.5±0.398	0.549±0.59	99.025±2.05
F5	5.0±0.28	0.562±0.88	99.145±2.14
F6	4.5±0.336	0.583±0.62	99.37±1.991
F7	6.0±0.225	0.539±0.91	98.774±2.19
F8	5.5±0.278	0.561±0.96	98.73±2.12
F9	5.0±0.356	0.574±0.55	98.83±2.053

Each value is represented as mean ± standard deviation (n = 3). Standard error of mean < 1.310

The *in vitro* drug dissolution study revealed that all tablet formulations released the drug up to 7 h. The tablet formulation F1 released 100 % of drug in 8 h only, whereas table formulation F2 released all drug in 9 h and tablet formulation F3 and F8 released complete drug in 10 h. The tablet formulations F4, F5, F6 and F7 released 100 % of drug from its dosage form within 7 h only. The more controlled release of drug was observed from Pioglitazone controlled release tablet formulation F9 (Containing HPMC K4M 80 mg and ethyl cellulose 75 mg) as it released it 100 % of drug up to 11 h.

From the release kinetics data Table 6, it was confirmed that, the control release formulations

F1 to F9 obeyed zero order kinetic model, independent of time and concentration. All the tablet formulations obeyed Korsemeyer and Peppas kinetic model which confirms the diffusion controlled release. The diffusion co-efficient data indicates that the tablet formulations F3 to F8 released the drug by diffusion following Fickian transport mechanism, whereas tablet formulations F1, F2 and F9 released the drug by diffusion following non-Fickian transport mechanism.

CONCLUSION

The controlled release of pioglitazone from the developed tablets will help to improve the therapeutic efficacy and patient compliance by reducing the dose and frequency of dosing of pioglitazone perhaps as *in vitro* study suggested 100 % release of drug over 11 hours period. Hence from the *in vitro* and *in vivo* studies, it could be concluded that the controlled release tablets of pioglitazone containing HPMC K4M (80 mg) and ethyl cellulose (75 mg) were found to be efficient and successful formulation for safe management of diabetes.

ACKNOWLEDGEMENT

Authors wish to thank Cipla Ltd., Baddi, Himachal Pradesh, India, for providing pioglitazone as gift sample. Authors also wish to thanks CPET, Bhubaneswar, for providing facility to carry out Instrumental study.

REFERENCES

[1] Sekiguchi K, Obi N. Studies on absorption of eutectic mixture I.A. comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 1961; 9: 866-872.

[2] Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci., 1971; 60: 1281-1302.

[3] Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS Pharm. Sci. Tech., 2006; 7(3): 68-73.

[4] Baylan S. Encycolpedia of Pharmaceutical Technology, volume 1. 2nd edition, Marcel Dekker Inc.; New York: 2002. pp. 1123-1129.

[5] Leunner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm., 2000; 50: 47-60.

[6] Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics A Treatise, 1st edition, Vallabh Prakashan; New Delhi: 1995. pp. 171-172.

[7] Crum CP. Diabetes, in: Cotran RS, Kumar V, Collins T, editors, Robbins, Pathologic Basis of Disease, 6th edition, Published by Harcourt (India) Private Limited; New Delhi: 1999. pp. 934-946.

[8] Rang and Dales Pharmacology, Antidiabetic drugs, Churchill Living Stone Elsevier; Philadelphia: 2007. pp. 696-678.

[9] Tripathi KD. Antidiabetic drugs, in: Essentials of Medical Pharmacology, 5th edition, Jaypee Brothers Ltd.; New Delhi: 2003. pp. 345-352.

[10] Jipkate AR, Chandrakant GB, Jadhav RT. Formulation and evaluation of Citicoline sustained release tablet. J. Pharm. Sci. Res., 2011; 3(1): 911-917.

[11] Guruswami S, Kumar V, Mishra DN. Characterization and *in vitro* dissolution studies of solid systems of valdecoxib with chitosan. Chem. Pharm. Bull., 54; 2006: 1102-1106.

[12] Babu PS, Ramu AS, Vidyadhara S. Enhancement of dissolution rate of glimepride using newer carriers. Indian Pharmacist, 69; 2008: 65-68.

[13] Lachman L, Liberman HA, Kanig JL. Tablets, in: The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House; Bombay: 1987. pp. 293-326.

[14] Martin A, Bustamante P, Chun AHC. Powder Rheology, Martin Physical Pharmacy, 4th edition, B.I. Waverly Pvt. Ltd.; New Delhi: 1994. pp. 465-466.

[15] Hirasawa N, Shise I, Miyata SH, Danjo K. Physiochemical characteristics and drug release studies of nilvadipine solid dispersions using water insoluble polymer as carrier. Drug Dev. Ind. Pharm., 2003; 29(3): 339-344.

[16] Rathinaraj BS, Rajveer C, Choudhury PK, Sheshrao BG, Shinde GV. Studies on dissolution behavior of sustained release solid dispersions of nimodipine. In J. Pharm. Sci. Rev. Res., 2010; 3(1): 77-82.

[17] MurliMohan GV. Controlled release of diclofenac sodium by gum karaya-chitosan complex coacervate *in vivo* Evaluation. Indian J. Pharm. Sci., 2001; 23: 408-412.

[18] The United States Pharmacopoeia. USP/NF, 25/20. (2002). The U. S. Pharmacopoeial Convention, Rackville, MD. pp: 2008-2012.

[19] Varshosaz J, Tavakoli N, Roozbahani P. Formulation and *In vitro* Characterization of Ciprofloxacin floating and bioadhesive extended-release Tablets. Drug Deliv., 2006; 13: 277-285.
[20] Higuchi T. Mechanism of rate of sustained-action medication. J. Pharm. Sci., 1963; 52 (7): 1145-1149.
[21] Ritger PL, Peppas NA. Modelling of water transport solute release in physiologically sensitive gels. J. Control Release, 1987; 5: 37-34.
[22] Jones D. Pharmaceutical Statistics, Pharmaceutical Press; London: 2002. pp. 315-333.
[23] Bolton S. Analysis of variance, In: Pharmaceutical Statistics Practical and Clinical Application. Marcel Dekker; New York: 1997.