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Original Article

In Vitro and In Vivo Evaluation of Controlled Release Tablets of Pioglitazone HCl Solid Dispersion

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ABSTRACT

Objective: The primary objective of the study is to enhance the bioavailability of drug, pioglitazone HCl by kneading technique using β-cyclodextrine as carrier in the ratios of 1:1, 1:2, 1:3 and 1:5 (F1 to F5) respectively. **Method:** The prepared kneaded complexes were characterized for drug content and *in vitro* drug release studies. The kneaded complex of pioglitazone (F1) is releasing 100 % drug within least time (45 min) with maximum drug content. The drug excipients 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 hardness, friability, drug content and *in vitro* drug dissolution studies. **Results:** *In vitro* experiments indicated a sustained release over 11 h in a controlled and constant manner with acceptable tablet parameters as per USP-NF for formulation T9. The *in vivo* (Antidiabatic) activity of the optimized controlled release tablet (F9) was evaluated in streptozocine induced diabetic model of Wistar rats using Nicotinamide as standard drug. **Conclusion:** 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 (11 h) both in case of *in vitro* and *in vivo* studies and can be adopted for a successful delivery of pioglitazone for oral use for safe management of diabetes.

Keywords: Pioglitazone HCl, β-cyclodextrin, kneading, antidiabetic, bioavailability, control release, *in vitro* and *in vivo*.

1. 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

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and polyethylene glycols are used as carriers for enhancement of aqueous solubilty[4-6]. 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].

2. 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. Streptozocine was procured from Sigma Aldrich, Germany. 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

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[11-13]. 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)[14,15]. 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 HPMCK4M 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).

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[17]. 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[18]. Reproducibility was checked by running the sample in triplicate

Quality control test on the tablets

Hardness

Hardness study was conducted by following the guidelines of the USP-NF, 2002[19]. 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) [19].

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[20].

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)[20]. 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.

***In vivo* (Antidiabetic) study**

Animals and drugs

Healthy Wister rats of either sex were used in the present study. *In vivo* evaluation studies of the optimized formulation and pure drug, pioglitazone were carried out on normal healthy Wister rats selected with average body weight of about 200– 250 g. They were housed individually in polypropylene cages, maintained under standard conditions (12-h light and 12-h dark cycle; 25±30°C; 35–60% humidity); the animals were fed with standard rat pellet diet and water. They were kept in fasting condition for 16 h and prior to experiment they were fed with excess water *ad libitum*. Animals were caged and all operations on animals were done in aseptic condition[21-24]. The streptozocine induced diabetic model was used to evaluate the blood sugar level reducing capacity of pioglitazone matrix tablet formulations. Here the blood sugar level of rats was induced by administration of streptozocine.

Experimental protocol

Animals were selected, weighed and divided into four groups (n=6), namely normal control, diabetic control, standard drug (pioglitazone) and optimized tablet formulation. Approval for the research work was obtained by the Institutional Animal Ethics Committee of the Dadhichi College of Pharmacy, Bhubaneswar, Odisha (Ethical Committee No. 1200/AC/08/CPCSEA).

Experimental method

Noninsulin-dependent diabetes mellitus (NIDDM) was induced in overnight fasted animals by the administration of inducing agent (streptozocin) at a single dose of 60 mg/kg by intraperitoneal injection, after 15 min of the intraperitoneal administration of nicotinamide was given at a dose of 120 mg/kg[21-24]. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after the injection. Each animal with a blood glucose concentration level above 250 mg/dL (13.8 mM) was considered to be diabetic and used in the experiments. Only the rats found with permanent NIDDM were used for *in vivo* evaluation studies.

Animals were divided into four groups of six rats each such as group 1 animals are normal control rats administered with normal saline water; group 2 animals are diabetic control rats administered with normal saline water along with standard drug, nicotinamide (60 mg/kg body weight); group 3 animals are diabetic rats administered with pure pioglitazone (4 mg/kg body weight); and group 4 animals are diabetic rats administered with optimized formulation (F9) of tablets (test sample) equivalent to the dose of the standard drug, 4-mg/kg body weight using intra-gastric tube. For the control (groups 1 and 2), the fasting was done overnight and water *ad libitum* was allowed. For group 3 and group 4, pure standard drug and tablets were administered orally in the morning following overnight fasting. No food and liquid except water *ad libitum* were given to the animals during the experiment. After collection of zero-hour blood sample, optimized formulation of tablets was administered orally through intragastric tube. Blood samples (0.1 mL) were withdrawn from the tail vein of the rats up to 12 h at 1 h interval. Plasma glucose levels were determined using OneTouch® Horizon™, Blood Glucose monitoring system, Life Can, Inc., Milpitas, USA[21-24].

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 [25, 26].

3. RESULTS AND DISCUSSIONS

Relatively high drug content was observed for each solid dispersion 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 Fig 1. 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 (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.

Table 1: Drug content and *in vitro* drug release study of various pioglitazone HCl kneaded complexes.

Formulations	Drug: carrier	Drug content (%) (X±S.D.)	Cumulative % drug release (X±S.D.)
F1	1:1	88.76±0.23	99.12±1.45
F2	1:2	85.61±0.14	98.58±1.21
F3	1:3	79.82±0.31	97.27±1.09
F4	1:5	78.02±0.19	96.96±1.11

Each value is represented as mean ± standard deviation (n = 3).
Standard error of mean < 0.837.

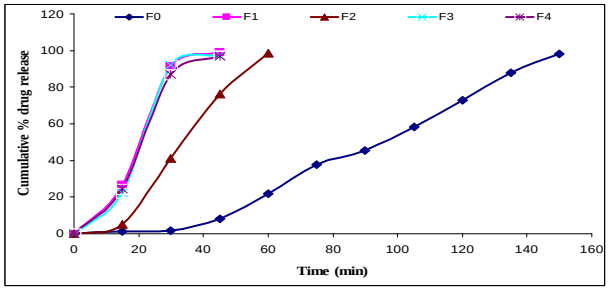

Fig 1: *In vitro* drug release profile of kneaded pioglitazone complex in 0.1N HCl.
F0 – Pioglitazone HCl pure drug.

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[27,28].

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**	**5**
Mg stearate	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Total weight	**280**	**280**	**280**	**280**	**280**	**280**	**280**	**280**	**280**

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.

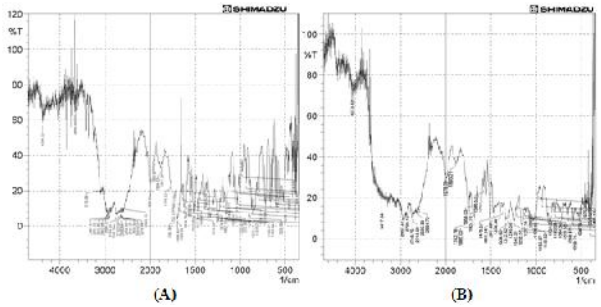

Fig 2: FTIR spectra of pure drug pioglitazone HCl and pioglitazone β-cyclodextrine kneaded complex in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

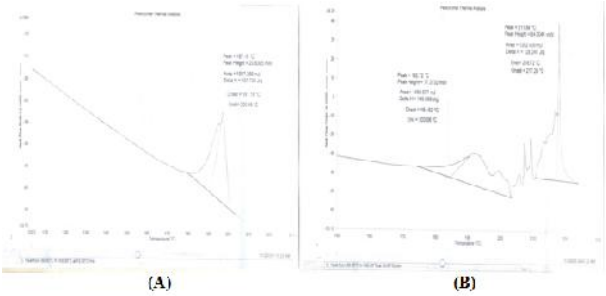

Fig 3: Differential scanning colorimetric study of pure drug, pioglitazone and pioglitazone - β-cyclodextrin inclusion complex.

The hardness of all tablet formulations was ranged from 5.0±0.28 to 6.0±0.356 kg/cm^2 (Table 3). 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 3.

Table 3: Hardness, friability and drug content 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.

Table 4: Antidiabetic activity of pioglitazone optimized matrix tablet formulation using streptozocine induced diabetic model.

Time (h)	Groups			
	1	2	3	4
	Blood glucose level (mM) (X±S.D.)			
0	5.2±0.34	19.1±0.41	19.2±0.52	19.0±0.44
1	5.6±0.58	19.6±0.75	18.4±0.81	19.3±0.38
2	5.5±0.62	19.5±0.92	13.8±0.85	17.4±0.59
3	5.9±0.88	19.8±1.13	11.4±1.02	12.5±0.92
4	6.1±0.48	18.9±0.83	6.9±0.72	11.4±0.92
5	5.8±0.22	19.2±0.66	8.2±0.55	9.6±0.54
6	5.6±0.37	19.1±0.59	15.8±0.49	9.8±0.92
7	6.4±0.58	19.2±0.71	16.9±0.22	7.5±0.60
8	5.4±0.61	19.2±0.33	17.3±0.75	7.1±0.31
9	5.2±0.77	19.4±0.84	17.7±0.62	5.1±0.49
10	5.8±0.49	19.7±0.93	17.5±0.72	5.0±0.92
11	5.9±0.51	19.2±0.72	18.1±0.59	4.9±0.38
12	5.5±0.38	19.4±0.63	15.9±0.61	4.8±0.58

Each values is represented as mean ± standard deviation (n = 6). Standard error of mean < 0.687. *P<0.05 (test of significance between two proportions by z-test) in comparison to control 12 h study. NS – Non-significant. Group 1 – Control (Normal saline water), group 2 – Diabetic control (Streptozocine – 60 mg/kg), group 3 – Streptozocine (60 mg/kg) with Pioglitazone 4 mg/Kg and groups 4 - Streptozocine (60 mg/kg) with optimized pioglitazone controlled release tablets (F9).

All the batches of tablets exhibited good uniformity in drug content (98.73±2.12 to100.04±2.27) as shown in Table 3. 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 (Fig 4). 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, where as the controlled release tablet 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.

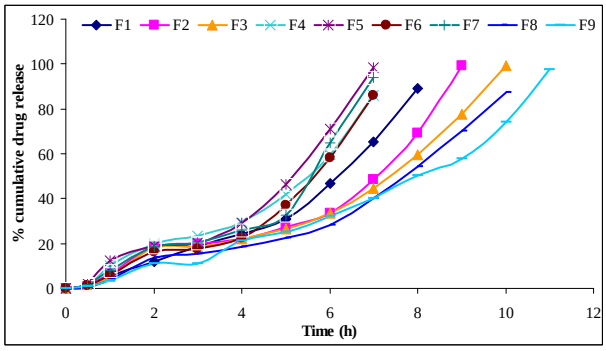

Fig 4: *In vitro* drug release profile of various pioglitazone controlled release tablet formulations

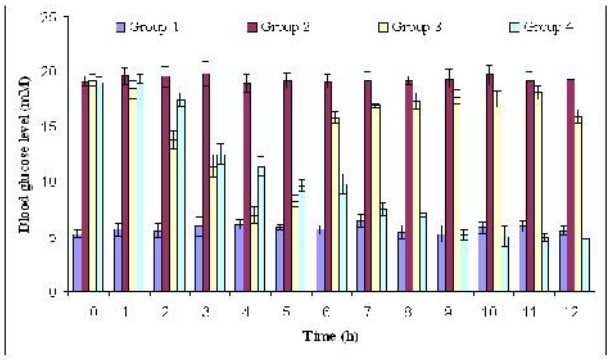

Fig 5: Comparison of *in vivo* plasma glucose levels in streptozocin-induced diabetic albino rats.

Group 1 – Control (Normal saline water), group 2 – Diabetic control (Streptozocine – 60 mg/kg), group 3 – Streptozocine (60 mg/kg) with Pioglitazone 4 mg/Kg and group 4 - Streptozocine (60 mg/kg) with optimized pioglitazone controlled release tablets (F9).

In vivo evaluation was carried out in healthy male Wister rats by measuring blood glucose level after oral administration with optimized pioglitazone tablets formulation (F9) of equivalent to the dose of the drug, 4-mg/kg body weight in comparison with administration of pure drug at the same dose level. The antihyperglycemic effect of formulation and pure standard drug in diabetic rats were assessed at different time intervals (Table 4 and Fig 5). Afterwards when pioglitazone solution (standard) was given orally, the blood glucose level started to decrease from the second hour. After the fourth hour, blood glucose level reached to almost normal level but after the fifth hour blood glucose level started to increase again. On the contrary, on oral administration of the optimized pioglitazone tablet formulation (F9), blood glucose level started to decrease from the third hour and this decrease continued up to the ninth hour until blood glucose reached to normal level. This was maintained up to the 12th h and blood glucose was found to be 4.86 mM. The lowering of blood glucose level was slower, as expected, in case of pioglitazone tablets than pure pioglitazone due to its higher dissolution rate in pure form in gastric fluid of the rats.

4. 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 h 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.

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