ISSN: 2231-6078

INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
1(3): July-September: (2011), 157-163

Research Article

Formulation and Evaluation of Pioglitazone Hydrochloride Matrix Tablet Containing Aloe Barbadensis Miller Mucilage Natural Antidiabetic Agent

Patidar Deepak*, Jain Abhishek, Jatav Rakesh K. and Sharma Hariharanand

Centeral India Institute of Pharmacy, Indore, M.P., India

Abstract

Matrix tablets of Pioglitazone hydrochloride to be taken once daily were formulated and characterized. Matrix system based on combination of aloe barbadensis miller leaf mucilage and polyvinylpyrrolidone in varying concentrations were studied to get the desired sustained release profile over a period of 24 h. The granules were evaluated for angle of repose, bulk density, compressibility index, and drug content. The granules showed satisfactory flow properties, compressibility and drug content. The release pattern of Pioglitazone hydrochloride was fitted to different models based on coefficient of correlation. Formulation (F5) containing aloe barbadensis miller leaf mucilage and polyvinylpyrolidone (12.50% w/w at 1:1 ratio) gave the desired release for once a day administration. The drug release was found to be diffusion controlled coupled with erosion having high correlation for Higuchi release pattern. The release pattern was close to the theoretical release profile.

Key words: Sustained release tablets, Pioglitazone hydrochloride, Evaluation of tablets

Introduction

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug delivery systems [1]. Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance [2, 3]. Matrix type sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pellitization during manufacturing and drug release from the dosage form. It is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form [4, 5].

Diabetes mellitus is a chronic metabolic disorder characterized by high glucose concentration in blood, caused by Insulin deficiency, often combined with Insulin resistance[6]. Pioglitazone hydrochloride is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus[7]. Pioglitazone hydrochloride is a basic (pKa = 12.06) which is practically insoluble in water and alkaline buffer solutions but as per the Biopharmaceutical Classification System (BCS) it is highly drug permeable (class 2). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimentation half-life of 3-7 h.

***Corresponding Author**
E-mail: deepak.patidar07@gmail.com

Pioglitazone hydrochloride is reported to have a short biological half-life requiring it to be administered in 2 to 3 doses of 15 to 45 mg per day[8]. Hence we have selected Pioglitazone hydrochloride for the development of once daily sustained release matrix tablets. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for Pioglitazone hydrochloride for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance.

The mucilage of Aloe barbadensis miller leaves clinically and experimentally proved anti-diabetic activity [9] and release retardant activity in the present study. The objective of present investigation is to design and evaluate sustained release tablets of Pioglitazone hydrochloride using Aloe barbadensis miller leaves mucilage and polyvinylpyrolidone combination as release retardant for making sustained release matrix tablets.

Material and Methods

Materials:

Pioglitazone hydrochloride was obtained as a gift sample from the Cadila Pharma Ltd., Dolka, Ahmadabad, India. The Aloe barbadensis Miller leaves were collected from the local areas of Indore, M.P. India. Di-basic calcium phosphate, Polyvinylpyrrolidone and Magnesium stearate were procured from Loba chemie, Mumbai, India. All other chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Method:

Extraction of mucilage:

The fresh Aloe barbadensis miller leaves were collected and washed with water. Incisions were made on the leaves and left over night. The leaves were crushed and soaked in water for 5–6 hours, boiled for 30 minutes and left to stand for 1 hour to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, grounded, passed through a # 80 sieve and stored in desiccator at 30°C & 45% relative humidity till use [10].

Drug polymer compatibility studies:

The pure drug and physical mixture of drug and polymers were subjected to IR spectroscopic study using FT-IR spectrophotometer (FTIR ABB MB3000). The spectra were scanned over the wave number range from 4000 – 400 cm^{-1},[11].

Calculation of Optimum release profile of Pioglitazone hydrochloride matrix tablet:

Optimum release profile for once daily SR formulation was calculated by the following equation using available pharmacokinetic data [12].

$$Dt = Dose\ (1+ 0.693 \times t / t\ ½)$$

Where Dt is total dose of drug, dose is dose of the immediate release part, t is time during which the sustained release is desired (24 h) and t ½ is half -life of the drug (3-7h). The optimum formulation was selected on the above equation so that it could attain complete and controlled drug release upon "trading off" various response variables; the following maximizing criteria were adopted.

Dt = 15(1 + 0.693 × 24/7)
= 50.64

Formulation of matrix tablet:
Sustained release matrix tablets of Pioglitazone hydrochloride with Aloe barbadensis Miller leaf mucilage and polyvinylpyrolidone were prepared by using different drug: mucilage ratios as shown in Table 1., Aloe barbadensis Miller leaves mucilage and polyvinylpyrolidone were used as matrix forming materials while Di-basic calcium phosphate as a diluent and magnesium stearate as a lubricant. All ingredients used were passed through a #100 sieve, weighed and blended. The granules were prepared by wet granulation technique and compressed by using single station hand operated table making machine.

Evaluation of granules:

Angle of repose (θ):
The frictional forces of granules can be measurement by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

Where, the θ is the angle of repose, h = height, r = radius

Bulk density:
Both loose bulk density (LBD) and tapped density (TBD) were determined. The accurately weighted amount of sample taken in a 25 ml measuring cylinder of Borosil measurement/recorded the volume of packing recorded and LDB and TBD calculated by following:

$$\text{LBD (loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Bulk Volume of Powder}}$$

$$\text{TAB (tapped bulk density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Powder}}$$

Hausner's ratio:
Flow properties of granules were determined by Hausner's ratio calculated by following formula:

$$H = \frac{\text{Tapped bulk density}}{\text{Lose bulk density}}$$

A Hausner ratio greater than 1.25 is considered of poor flow ability.

Carr's Index:
Percentage compressibility of granules was determined by carr's compressibility index calculate by following formula [13].

$$\text{Carr's Index} = \frac{\text{TBD - LBD}}{\text{TBD}}$$

Evaluations of tablets:

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

Friability:
The Friability of the tablet 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 4 mins. The tablets were weighed again (W_{final}). The % friability was then calculated by:-

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X100$$

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

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%.

Drug Content:
An accurately weighed equivalent amount 100 mg of Pioglitazone hydrochloride into the matrix tablets. Extracted with 0.1 N HCl and the solution was filter. The absorbance was measured at 270 nm after suitable dilution.

Swelling behavior of matrix tablets:

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation F-1, F-2, F-3, F-4 and F-5 were studied. One tablet from each formulation was kept in a petridish containing phosphate buffer of pH 7.4. At the end of 2 hours, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 1 hour till the end of 6 hours. The % weight gain by the tablet was calculated by equation.

$$S.I = \left\{ \frac{(M_t - M_0)}{M_0} \right\} \times 100$$

Where, S.I = Swelling Index, M_t = Weight of tablet at time 't' and M_0 = Weight of tablet at time zero.

***In-vitro* drug release studies:**
Release of Pioglitazone hydrochloride from the matrix tablets was studied in phosphate buffer of pH 7.4 (900 ml) for 12 hrs using USP single station Dissolution Rate Test Apparatus (Joyti scientific industry, Gwalior) with a rotating paddle stirrer at 50 rpm and 37° ± 0.5°C. A. Samples of dissolution fluid were withdrawn through a pipette at different time intervals and were assayed at 265 for Pioglitazone hydrochloride content using a UV/visible spectrophotometer (Simadzu 1800). The drug release experiments were conducted in triplicate (n=3). The *in- vitro* release rates were showed in Figure. And this dissolution data was further treated for kinetic modeling [14].

Stability study:
The F5 formulation was subjected to stability at 30°C/65% RH and 40°C/75% RH for 3 month and evaluated for their physical

appearance, Hardness, Weight variation drug content and cumulative % drug release at specified intervals of time. [15]

.

Table 1: Composition of Matrix Tablets of Pioglitazone hydrochloride.

Ingredients	Formulation code (in mg)				
	F1	F2	F3	F4	F5
Pioglitazone hydrochloride	50	50	50	50	50
Aloe barbadensis Miller	2.5	5	7.5	10	12.5
Di-basic calcium phosphate	2.5	5	7.5	10	12.5
Polyvinyl pyrrolidone	140	135	130	125	120
Magnesium sterate	5	5	5	5	5
Total	200	200	200	200	200
% of Aloe barbadensis Miller	1.25	2.5	3.75	5	6.25

Figure 1: FTIR Spectrum of Pioglitazone Hydrochloride (Pure Drug).

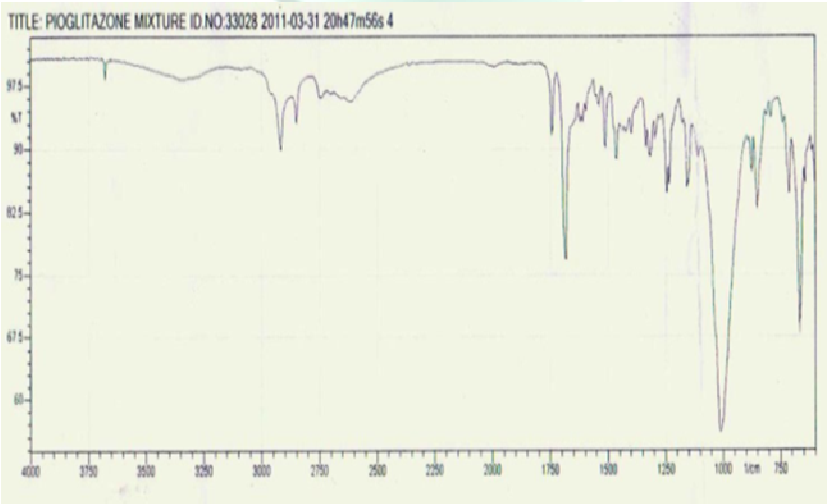

Figure 2: FTIR Spectrum of Pioglitazone Hydrochloride and Excipients mixture

Results and discussion

Evaluation of granules:

Table 2 shows the results obtained for angle of response of all the formulation. Angle of response (θ) values were found to be in the range of 27.87 ^{o} to 32.69^{o} respectively. All formulations showed the angle of repose good. Bulk Density, both loose bulk density (LBD) and tapped density for all the formulations varied from 0.085 gm/cm^3 respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder. Hausner's ratio were found to be in the range of 1.13 to 1.14. All the formulations showed the hausner's ratio less than 1.25. Percentage compressibility of granules was determined by Carr's compressibility index. The percentage compressibility for all the six formulations lies within the range of 11.83 to 12.65. Formulations F2 and F4 are showing to excellent compressible index and formulation F1, F3, and F5 showing fair to passable

Evaluation of tablets:

Result for evaluation of tablet for all the formulation is tabulated in table 3. The percentage weight variation for tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits of 5%. It was found to be form 198.85 mg to 200.05mg. The weight of all the tablets was found to be uniform. The thickness of tablets was measured by using vernier caliper by picking the tablets randomly. The mean values are shown in table 3. The values are almost uniform in all formulations. Thickness was found in range from 1.89 mm to 1.92 mm respectively. The hardness was maintained to be within 5.7 kg/cm^2 to 6 kg/cm^2. The friability study results was found in the range from 0.33 % to 0.67 %.

The content uniformity was performed for all the six formulations and results for drug content of the tablets was found "between" (97.86% to 99.53%) of Pioglitazone hydrochloride. The results indicated that all formulations the drug content was uniform.

Table 2: Evaluation of granules.

Formulation Code	Angle of Repose(θ)	Loose Bulk Density	Tapped Bulk Density	Hausner's Ratio	Carr's Index
F1	32.69±0.95	0.614±0.004	0.700±0.005	1.14±0.014	12.29±1.15
F2	29.86±0.69	0.612±0.011	0.697±0.005	1.13±0.013	12.23±1
F3	29.74±0.50	0.612±0.004	0.700±0.005	1.14±0.008	12.65±0.66
F4	28.74±0.44	0.609±0.007	0.694±0.009	1.13±0.015	12.19±1.15
F5	27.87±0.43	0.612±0.004	0.694±0.009	1.13±0.017	11.83±1.37

Each data represents mean ± SD (n=3)

Table 3: Evaluation of tablets

Sr. No	Formulation code	Uniformity of weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	F1	199.65±2.25	1.92±0.04	5.7±0.11	0.33±0.19	99.53±0.70
2	F2	199.55±1.90	1.91±0.05	5.8±0.08	0.57±24	98.06±0.30
3	F3	200±1.68	1.9±0.05	6±0.17	0.57±0.10	97.86±0.30
4	F4	200.05±1.98	1.91±0.04	6±0.15	0.53±0.31	99.33±0.41
5	F5	198.85±1.46	1.89±0.05	6±0.20	0.67±0.12	99.33±0.41

Each data represents mean ± SD (n=3)

Swelling index:
The swelling index of tablet was performed in the terms of percentage weight gain by matrix tablet shown in figure 3.

***In-vitro* release studies:**
All the five formulations were subjected for the *in vitro* dissolution studies using dissolution apparatus USP II. The samples were taken at hourly intervals and analyzed at 265 nm. Pioglitazone hydrochloride matrix tablet, formulation F1 to F5 formulated with various percentage of Aloe barbadensis miller leaf mucilage, the *In-vitro* dissolution data were treated using zero order, first order, Higuchi plot, and Korsmeyer Peppa's plot Model were shown in figure 3, 4, 5 and 6 respectively. The kinetic plots were perfectly fitting to the formulated Aloe barbadensis miller leaf mucilage- Pioglitazone hydrochloride matrix tablets the kinetics value regression coefficient (r), slop (n), and rate constant are shown in the table 5

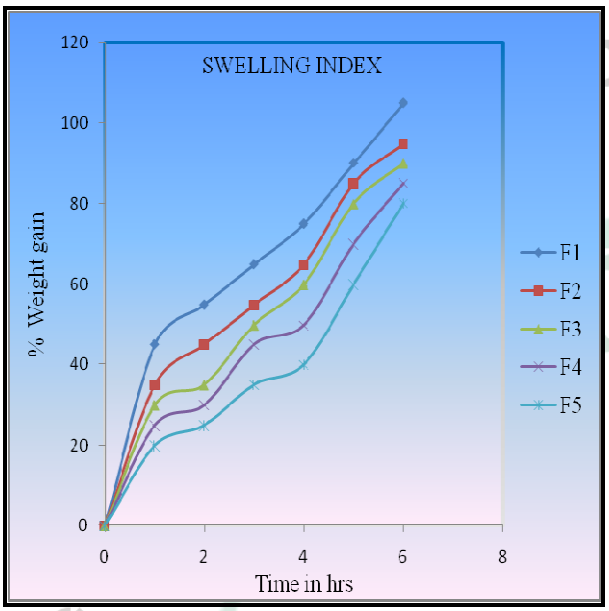

Figure 3: Swelling behaviour of tablet formulation.

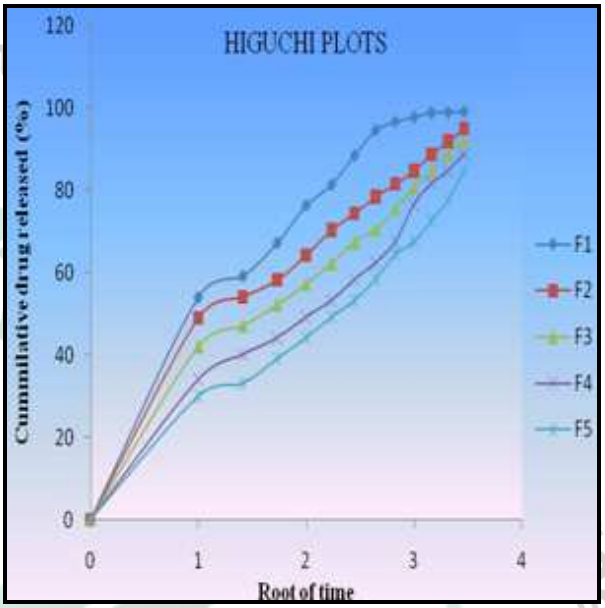

Figure 5: Higuchi plots of F1 to F5

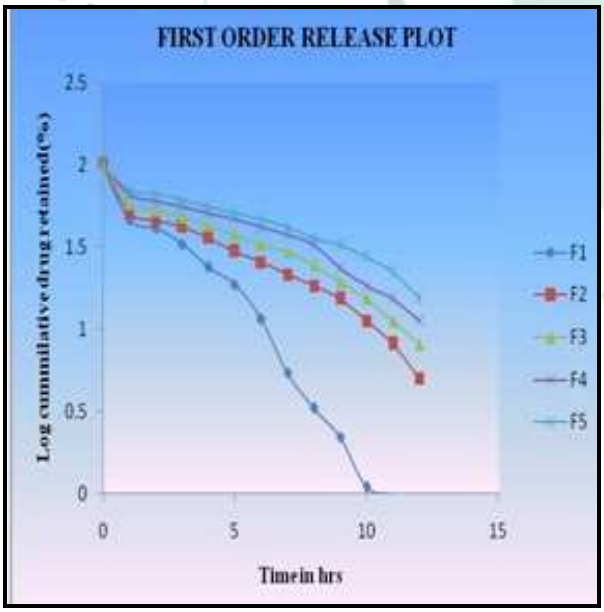

Figure 4: First order release plots of F1 to F5

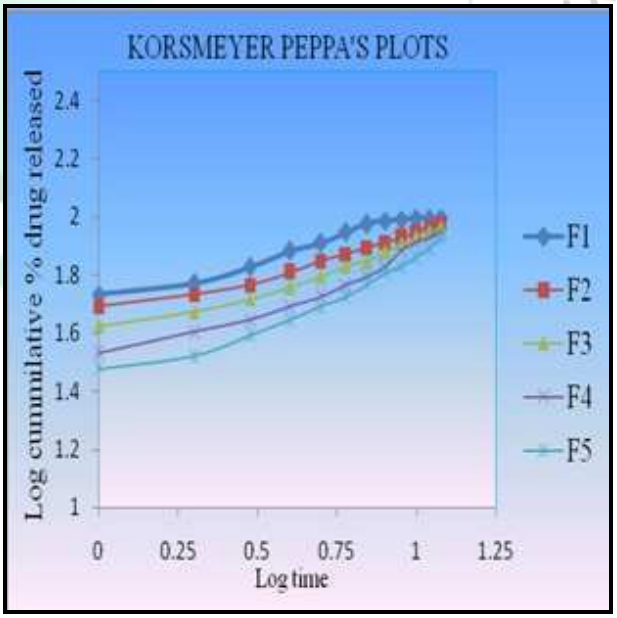

Figure 6: Korsmeyer Peppa's Plots for F1 to F5.

Formulation code	Zero order			First order			Higuchi's		Korsmeyer Peppa's	
	Slope	Rate constant (K^0 = -Slope)	Regration Coefficient (r)	Slope	Rate constant (K = - Slope× 2.303)	Regration Coefficient (r)	Slope	Regration Coefficient (r)	Slope	Regration Coefficient (r)
F1	6.179	-6.179	0.724	-0.179	0.412	0.979	26.95	0.923	0.281	0.967
F2	5.743	-5.743	0.786	-0.089	0.204	0.959	24.38	0.949	0.282	0.971
F3	5.857	-5.857	0.852	-0.077	0.177	0.96	24.2	0.974	0.332	0.964
F4	6.019	-6.019	0.914	-0.069	0.015	0.952	24.07	0.979	0.452	0.948
F5	5.711	-5.711	0.931	-0.056	0.12	0.954	22.67	0.983	0.435	0.954

Table 5: Kinetic values obtained from in-vitro release profile.

Stability studies:

Stability studies of best formulation F5, showed no significant change in % drug content and dissolution profile in the applied condition of temperature and humidity 30 ºC / 65% RH, & 40 ºC / 75% RH for a period of 3 months.

Conclusion

In conclusion, following the parameters of matrix tablets were within acceptable official limits. Pre-compressional parameters angle of repose, % compressibility and Hausner's ratio are in the range of given in official standard, indicated that granules prepared by wet granulation method were free flowing. The post-compression parameters of matrix tablets (hardness, friability, weight variation, thickness and drug content) were within the acceptable official limits.

The present study revealed that Aloe barbadensis miller leaves mucilage and polyvinylpyrolidone combination appears to be suitable for use as a release retardant in the manufacture of sustained release matrix tablets because of its good swelling, good flow and suitability for matrix formulations. From the dissolution study, it was concluded that dried Aloe barbadensis miller leaves mucilage in combination with polyvinylpyrolidone forms a good matrix for sustained release of drug from the tablets.

This Aloe barbadensis Miller mucilage for controlling the release rate of Pioglitazone hydrochloride has been developed. This type of system provides a significant and convenient method for achieving controlled release in oral dosage forms. The release of the drug form matrix tablets containing 1.25, 2.5, 3.75, 5, & 6.25 % of polymer was release drug 98.59, 94.52, 91.81, 89.05, & 83.65 % Cumulative release within 12 hrs.

The F5 batch tablets formulation were selected for the Stability studies were carried out according to ICH guidelines at 30°C & 65% RH and 40°C & 75% RH for three months indicated that the pure drug was stable in layered tablets.

References

1) Gwen MJ, Joseph RR. In: Banker GS and Rhodes, CT, Modern pharmaceutics. 3rd ed. Vol 72. New York: Marcel Dekker Inc., 1996; pp. 575.
2) Chein YW. Novel drug delivery systems. 2nd ed. New York: Marcel Dekker Inc., 1997; pp.1-42.
3) Ritchel WA. Biopharmaceutic and pharmacokinetic apects in the design of controlled release per-oral drug deliver system. Drug Dev Ind Pharm 1989; 15: 1073-103.
4) Reddy KR, Mutalik S, Reddy S. Once daily sustained release matrix tablets of nicorandinal formulation in vitro evaluation. AAPS Pharm Sci Tech 2003; 4: 1-9.
5) Mohammed AD, James LF, Michael HR, John EH, Rajabi-Siahboomi AR. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and hydroxypropylmethylcellulose. Pharm Dev Tech 1999; 4: 313-24.
6) Nolte, M.S., karam, J.H., Pancreatic hormones and anti-diabetic drugs, in Katzung BG (eds), Basic and Clinical pharmacology, 8th edition., lange Medical books/ Mc Grew-Hill Publishing Devision, New York, 2001, pp 711-734.

7) Theodore WR, Alan SN, Taylor P, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed, New York, NY: McGraw-Hill; 1991; pp1484
8) Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY: McGraw-Hill; 1991: pp 1712.
9) Boudreau MD, Beland FA, An evaluation of the biological and toxicological properties of Aloe barbadensis (miller), Aloe barbadensis Miller, Journal of environmental science and health. Part C, Environmental carcinogenesis & ecotoxicology reviews, 2006, 24 (1); 103–54.
10) Sreeramulu J, Hima Bindu V, Kumar CS, Kumar Reddy BK, "Fabrication and Evaluation of Glipizide Aloe barbadensis miller Leaf Mucilage Polyvinylpyrolidone Controlled Release Matrix Tablets" Journal of Pharmacy Research, 2010; 3(7):1569-1572
11) Kavitha K, Puneeth KP, Tamizh MT, "Development And Evaluation Of Rosiglitazone Maleate Floating Tablets" International Journal of Applied Pharmaceutics 2010; Vol 2 (2).
12) Wakode R and Bajaj A, 2010 "Formulation and Development Of Once A Daily Sustained Release Matrix Tablet For Pramipexole" IJPI's Journal of Pharmaceutics and Cosmetology 1.
13) Radhikaa PR, Pala TK, Sivakumar T, "Formulation and Evaluation of Sustained Release Matrix Tablets of Glipizide" Iranian Journal of Pharmaceutical Sciences" 2009; 5(4) 205-214.
14) Abdul Ahad H, Kumar CS, Kumar K, Reddy B, Kumar AB, "Preparation and evaluation of sustained release matrix tablets of gliquidone based on combination of natural and synthetic polymers" Journal of Advanced Pharmaceutical Research, 2010; 1(2): 108-114