International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE **V-1, I-2, 2012**

Formulation & Evaluation of Once Daily Sustained Release Matrix Tablet of Pramipexole Dihydrochloride

Patel NA[*1], Makwana ST[1], Patel ZP[1], Solanki SM[1], Patel MB[1]
[1]*Department of Pharmaceutics, K.B.Raval College of Pharmacy, Shertha, Gandhinagar, Gujarat, India*
Manuscript No: IJPRS/V1/I2/00108, Received On: 31/05/2012, Accepted On: 16/06/2012

ABSTRACT

The objective of this study was to formulate & evaluate sustained release matrix tablet of Pramipexole Dihydrochloride. Pramipexole Dihydrochloride being highly water soluble drug so, hydrophilic matrices alone are not able to control the drug release for 24 hours. Matrix forming agents like hydroxyl propyl methyl cellulose, rosin & glyceryl behenate in varying concentrations were studied to get the desired sustained release profile over a period of 24 hours. The granules were evaluated for bulk density, angle of repose, compressibility index. Matrix tablets were evaluated for weight variation, hardness, friability & *in-vitro* release. Release profile of F11 with 15% gum rosin and 25% glyceryl behenate was found to be 99.7% in 24 hrs which was considered as the optimized formulation. Release profile of formulation F11 was found to be very close to theoretical profile of Pramipexole. The drug release followed zero order and found to be diffusion controlled with erosion having high correlation for Higuchi related pattern.

KEYWORDS

Sustained release, Matrix tablets, Rosin, Glyceryl behenate, Pramipexole dihydrochloride, Higuchi release.

INTRODUCTION

Oral sustained release systems continue to dominate the market despite the advancements made in other drug delivery systems in order to increase the clinical efficacy and patient compliance. From a practical pharmaceutical view point, numerous types of polymers are currently employed to control the drug release from the pharmaceutical dosage form. Oral sustained release systems are mainly grouped into three types, e.g. reservoir, monolithic & matrix types[1,2].

Various natural gums and mucilages have been examined as polymers for sustained drug release, in the last few decades[3,4].

***Address for Correspondence:**
Patel Nishi A.
Department of Pharmaceutics,
K.B.Raval College of Pharmacy, Shertha, Gandhinagar,
Gujarat, India.
E-Mail Id: rxnishi@gmail.com

Natural polymers are biodegradable and generally nontoxic in nature, readily available, capable of multitude of chemical modifications. One such biopolymer is rosin. Rosin and its derivatives have been pharmaceutically evaluated as matrix forming agent, microencapsulating materials, as anhydrous binding agents in tablets, as film coating materials, as transdermal drug delivery[5].

Waxes have also been extensively investigated for sustaining the release of drugs[6]. A waxy polymer can minimize the problem which are associated with hydrophilic polymer and highly water soluble drug. Glyceryl behenate (Compritol 888 ATO) is a waxy polymer, which has recently had a wide application as a sustained release polymer[7]. It is used as a lubricant and binding agent for tablets in concentration of 1-3% and a sustained release

excipient in concentration between 10% to 50%[8].

Parkinson's disease is a neurodegenerative condition characterized by tremor, bradykinesia, rigidity, and postural instability[9]. Pramipexole has been investigated as a monotherapy in the treatment of early & advanced Parkinson's disease. In advanced Parkinson's disease the usual dose of Pramipexole is as high as 1.5 mg three to four times a day.

The half life of Pramipexole is 8 hours & is highly soluble in water & belongs to BCS class 1. The drug release of highly water soluble drug is mainly modulated by polymeric matrix system. The drug release for extended duration, for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms[10]. Hence, in the present work, an attempt has been made to develop once-daily sustained-release matrix tablets of Pramipexole using hydrophilic matrix materials such as hydroxyl propyl methyl cellulose (HPMC), hydrophobic matrices such as gum Rosin & Glyceryl behenate and hydrophilic polymer Poly vinyl pyrrolidone (PVP), were used as granulating agents. The developed sustained release matrix tablets will help in reducing the frequency of dose administration, & this will reduce severity of motor fluctuations and other side effects caused due to Pramipexole.

MATERIALS AND METHODS

MATERIALS

Pramipexole dihydrochloride was obtained as a gift sample from Cadila HealthCare Ltd., Ahmedabad. Glyceryl Behenate (Compritol 888 ATO) was obtained as a gift sample from Cadila HealthCare Ltd., Ahmedabad. Gum Rosin was procured from local market. All the other chemicals used were of analytical grade & were used as received.

METHOD OF PREPARATION

Sustained Release matrix tablets of Pramipexole dihydrochloride were prepared by wet granulation. Drug and excipients such as HPMC K4M, gum rosin, glyceryl behenate & lactose monohydrate were blended together. The alcoholic solution of PVP K 30 M (8 %w/v) was added to produce damp mass. The wet mass was passed through # 22 sieve and dried in hot air oven at 60ºC for 2 hrs. The dried granules were then passed through # 40 and mixed with lubricants. Prepared granules were compressed using rotary tablet punching machine. The tablets were evaluated in terms of drug content drug release profiles and other physicochemical parameters. The average weight of tablet was 250 mg with 5-6 Kg/cm^2 hardness. The dose for sustained release was calculated by Robinson equation by using the available pharmacokinetic data:

$$\mathbf{Dt = Dose\ (1 + 0.693 \times t/t_{1/2})}$$

Where, Dt = total dose of drug; Dose = dose of the immediate release part (1.5 mg); t = time (hours) during which the sustained release is desired (24 hours); $t_{1/2}$ = half-life of the drug (8 hours).

$$\mathbf{Dt = 1.5\ (1+ (0.693 \times 24)/8) \approx 4.5\ mg}$$

The formula of matrix based sustained release tablets of Pramipexole are given in table 1.

Calibration Curve of Pramipexole Dihyrochloride

An ultraviolet (UV) spectrophotometric method based on measurement of absorption at 262 nm in Phosphate buffer pH 6.8 was used for the estimation of Pramipexole dihydrochloride. The method showed very good linearity (r^2 value: 0.9987) in the concentration range of 2-12 µg/ml.

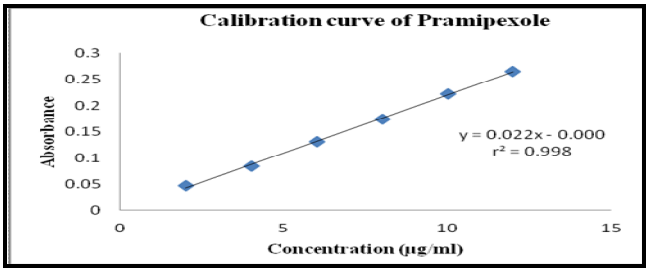

Table 1: Formula for Sustained Release Matrix Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Pramipexole Dihydrochloride	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
HPMC K4M	100	40	40	40	40	40	40	40	40	40	40
Gum Rosin	-	30	40	50	50	75	100	20	37.5	50	37.5
Glyceryl behenate	-	-	-	-	-	-	-	30	37.5	75	62.5
PVP K-30 (8%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lactose monohydrate	133	163	153	143	143	118	93	107	118	68	93
Magnesium Stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	5	5	5	5	5	5	5	5	5	5	5

Evaluation of Granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] X 100 / TBD

Evaluation of Tablets

Weight Variation Test

20 tablets of each formulation were weighed using an electronic balance (Metler Toledo), and the test was performed according to the official method.

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester and the Roche friabilator respectively.

Drug Content

For determining the drug content, 20 tablets were crushed and powdered in a mortar. The powder equivalent to 4.5 mg of drug was accurately weighed and transferred to 50 ml volumetric flask. The drug was extracted into diluent (phosphate buffer pH 6.8) by sonication for 30 min. The solution was filtered through watmann filter paper after making up the volume. Five ml of this solution was diluted to 10 ml with diluent and analyzed by UV Spectrophotometer at 262nm using phosphate buffer pH 6.8 as a blank.

Table 2: Evaluation of Granules

Formulation	Angle of Repose	Tapped density (g/ml)	Bulk Density (g/ml)	Compressibility index
F1	32.60 ± 0.09	0.647 ± 0.04	0.493 ± 0.03	19.80 ± 0.06
F2	30.09 ± 0.11	0.641 ± 0.07	0.496 ± 0.07	22.08 ± 0.08
F3	31.22 ± 0.08	0.636 ± 0.03	0.505 ± 0.05	20.59 ± 0.07
F4	34.04 ± 0.05	0.643 ± 0.08	0.501 ± 0.04	25.08 ± 0.09
F5	29.68 ± 0.12	0.635 ± 0.13	0.497 ± 0.06	21.73 ± 0.07
F6	30.57 ± 0.07	0.639 ± 0.06	0.501 ± 0.05	21.59 ± 0.06
F7	31.24 ± 0.04	0.647 ± 0.04	0.495 ± 0.08	20.49 ± 0.13
F8	31.07 ± 0.07	0.632 ± 0.06	0.498 ± 0.07	21.20 ± 0.08
F9	30.26 ± 0.06	0.639 ± 0.05	0.496 ± 0.06	22.37 ± 0.09
F10	29.47 ± 0.04	0.632 ± 0.11	0.498 ± 0.04	21.22 ± 0.11
F11	32.58 ± 0.08	0.644 ± 0.04	0.491 ± 0.05	19.75 ± 0.08

Table 3: Evaluation of Tablets

Formulation	Weight variation (mg)	Hardness ($kg/cm^{2)}$	Thickness (mm)	Friability (%)	Drug content
F1	252.3± 0.13	5.4 ± 0.43	2.22 ± 0.03	0.73	97.9 ± 0.17
F2	249.6 ± 0.11	6.1± 0.72	2.18 ± 0.05	0.58	98.2 ± 0.23
F3	251.4 ± 0.17	5.7 ± 0.31	2.24 ± 0.02	0.85	98.6 ± 0.19
F4	248.3 ± 0.05	5.9 ± 0.08	2.21 ± 0.04	0.54	97.7 ± 0.34
F5	251.4 ± 0.12	5.5 ± 0.24	2.23± 0.02	0.67	99.2 ± 0.27
F6	250.4 ± 0.07	6.2± 0.60	2.22 ± 0.05	0.49	98.8 ± 0.16
F7	252.1 ± 0.14	5.9 ± 0.44	2.20 ± 0.06	0.75	101.3 ± 0.32
F8	251.6 ± 0.08	5.7 ± 0.36	2.23 ± 0.03	0.62	99.6 ± 0.45
F9	249.5 ± 0.06	6.1 ± 0.14	2.19 ± 0.06	0.56	100.8 ± 0.18
F10	248.6 ± 0.04	5.6 ± 0.11	2.21 ± 0.05	0.64	98.7 ± 0.26
F11	252.3 ± 0.05	5.8 ± 0.23	2.23 ± 0.03	0.69	99.5 ± 0.29

In-vitro Drug release

In-vitro drug release studies were carried out using the USP type I dissolution test apparatus. Operating conditions were maintained at 37± 0.5ºC, basket speed was 100 rev/min, the dissolution medium was phosphate buffer pH 6.8 volume being 500 ml. Samples of 5 ml were withdrawn at every hour and same amount of dissolution medium was replaced. Aliquots were filtered using watmann filter paper and analyzed by UV spectrophotometer at 262nm. The studies were done in triplicate. On the basis of release studies the formulation which gave desired once a day release of Pramipexole was chosen as the optimized formulation. The dissolution profiles of different formulations are shown in figure 1, 2 & 3.

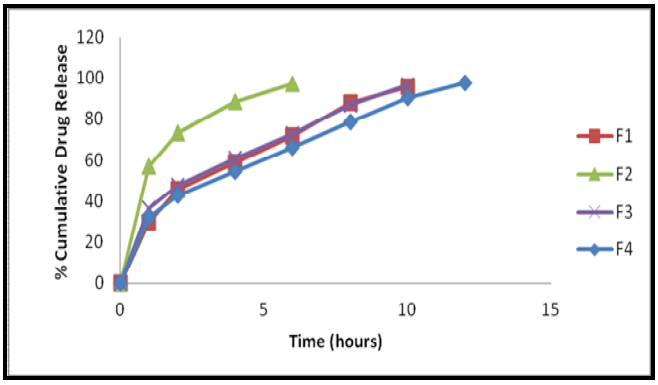

Figure 1: *In vitro* release profiles of Pramipexole formulations (F1 – F4)

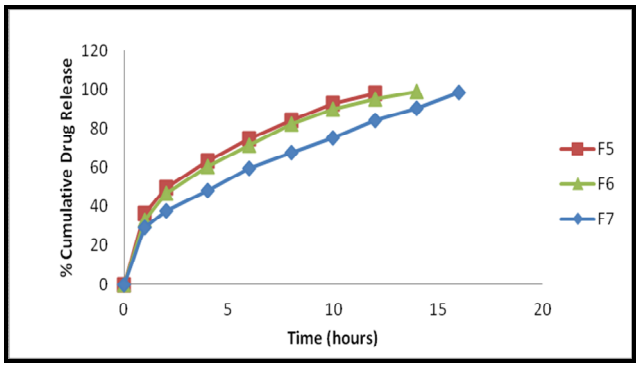

Figure 2: In vitro release profiles of Pramipexole formulations (F5 – F7)

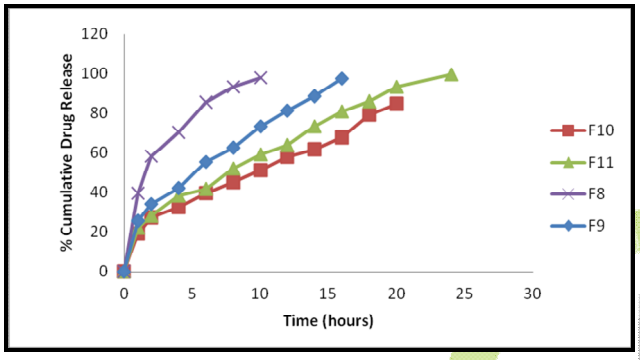

Figure 3: *In vitro* release profiles of Pramipexole formulations (F8 – F11)

Table 4: Theoretical release of Pramipexole formulation

Time(hours)	% Pramipexole released
1	<25
6	30-60
12	55-75
24	>80

Drug Release Kinetics

To determine the mechanism of drug release from this formulation, the drug release data of *in-vitro* dissolution study was analyzed with various kinetic equations. The data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), and Korsmeyer et al's (log cumulative percentage of drug released vs log time) equations along with zero order (cumulative amount of drug released vs time) pattern. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the obtained plots. The results are shown below.

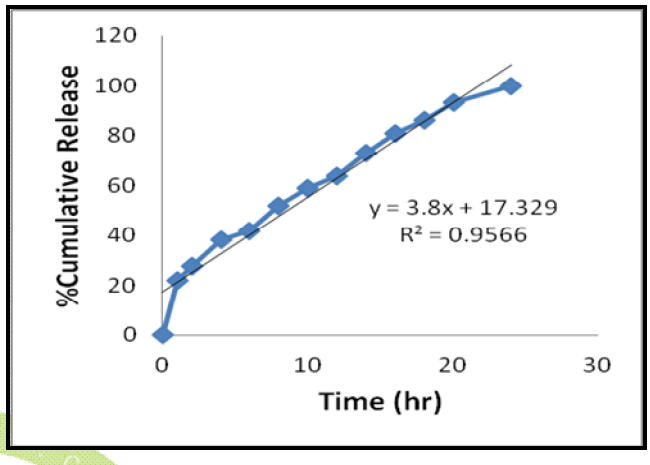

Figure 4: Zero order Plot

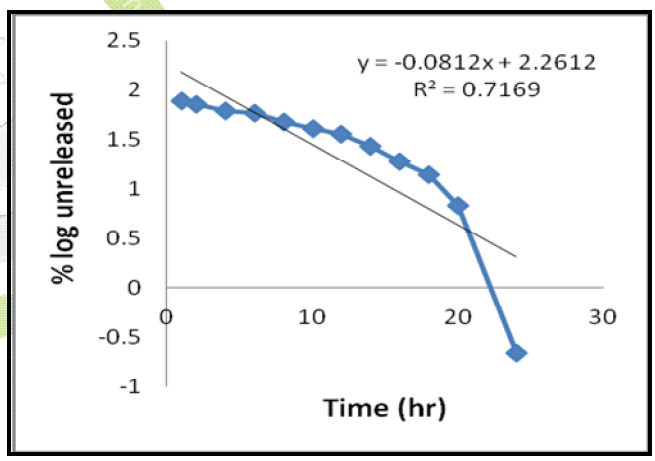

Figure 5: First order Plot

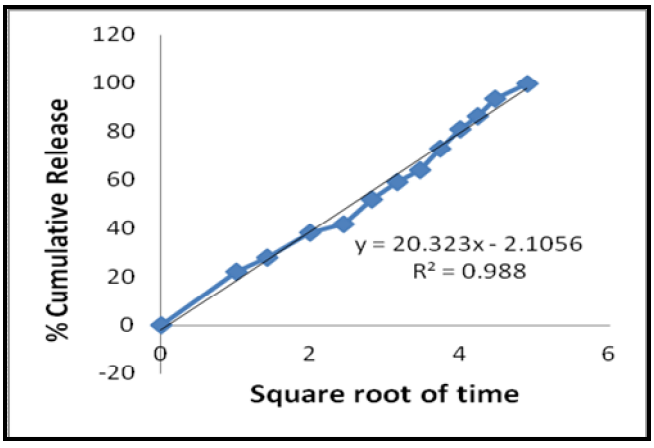

Figure 6: Higuchi Plot

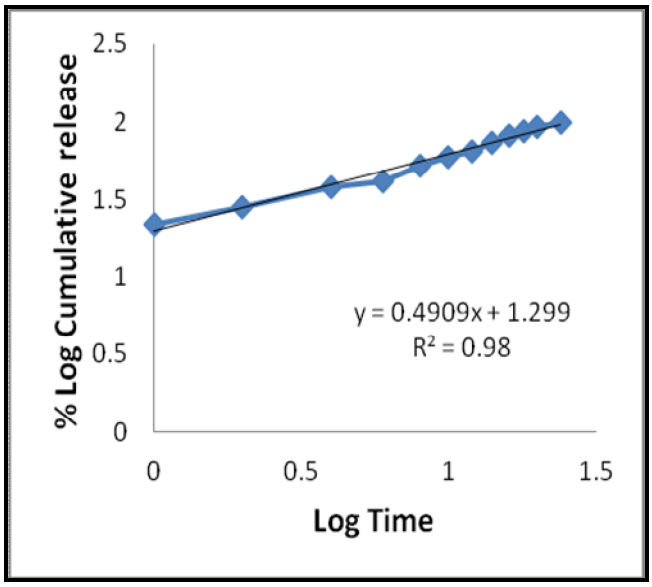

Figure 7: Korsemeyer Plot

Table 5: Data analysis by using different Release Kinetic Models of F11

Para-meter	Zero Order	First Order	Higuchi Plot	Korsemeyer-Peppas	
				r^2	n
Correlation Coefficient (r^2)	0.956	0.716	0.988	0.980	0.490

The drug release followed zero order as it showed fair linearity (R^2= 0.956, Table 5). The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2 = 0.988, Table 5). To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas's equation. The formulations F11 showed linearity (R^2: 0.980, Table 5), with slope (n) values ranging from 0.490. The mean diffusional exponent values (n) 0.490 indicated non fickian diffusion (anomalous transport). Zero order release is achieved from these matrices. From the above data analysis by using different model, Higuchi model was best fitted with linearity value 0.988.

RESULTS AND DISCUSSION

In the present study an attempt has been made to formulate matrix tablets of Pramipexole dihydrochloride using rosin & glyceryl behenate as hydrophobic matrix material. The pre compression parameters like bulk density, angle of repose & compressibility index reveal that the powder mixture had good flow properties, the results are shown in Table 2. Post compression parameters for all formulations are shown in Table 3. All the tablets were found to pass the uniformity of weight. Content of Pramipexole dihydrochloride from all formulations was found in the range of 97.9 to 101.3%. The hardness of tablets from all formulations was between 5.4 and 6.2 kg/cm^2. All the formulations showed friability between 0.49 and 0.85% indicating that the tablets could withstand the mechanical shock.

It was observed that the amount of polymer influences the drug release. In vitro release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration. The in vitro drug release characteristics were studied in phosphate buffer pH 6.8 for a period of 24 hours using USP dissolution apparatus 1. Formulation F1 containing high concentration of hydrophilic polymer released drug at faster rate, 90% releases in 8-10 hrs. Formulation F2, F3 and F4 released drug slowly as compared to formulation F1, F2 released about 97 % in 6 hrs, F3 released about 96% in 10 hrs & F4 released about 97% in 12 hrs. Rosin alone was used in F2, F3 & F4 with increasing concentration & it was observed that very high concentration of rosin gave very sticky mass which was difficult to handle. Formulation F5, F6, F7 released about 98.2%, 99.3% & 98.8% in 12, 14 & 16 hrs respectively. Therefore combination of rosin & glyceryl behenate was used in varying concentrations. Formulation F8 containing 8% rosin & 12% glyceryl behenate released 97.7% in 10 hrs. Formulation F9 containing (50:50) 15% rosin & 15% glyceryl behenate released 97.6 in 16 hrs. Formulation F10 containing high concentration of rosin & glyceryl behenate

released about 84.5% in 20 hrs. Release profile of F11 with 15% gum rosin and 25% glyceryl behenate was found to be 99.7% in 24 hrs which was considered as the optimized formulation. Release profile of formulation F11 was found to be very close to theoretical profile of Pramipexole. The drug release followed zero order release and higuchi release pattern with anomalous transport revealing non fickian diffusion having diffusion coupled with erosion.

CONCLUSION

The approach of the present study was to make an evaluation of sustained release matrix for highly water soluble drug, Pramipexole dihydrochloride. The hydrophilic matrix of HPMC alone could not control the release of Pramipexole effectively for 24 hours. It is evident from the results that a matrix tablet prepared with HPMC & hydrophobic polymers rosin (15% w/w) & glyceryl behenate (25% w/w) with PVP K-30 as a granulating agent is a better system for once-daily sustained release of a highly water-soluble drug like Pramipexole.

ACKNOWLEDGEMENT

The authors express sincere thanks to Cadila Healthcare Ltd. (Ahmedabad) for providing gift sample of Pramipexole dihydrochloride & Glyceryl behenate.

REFFERENCES

1. Lachman L, Liberman HA, Joseph LK. The Theory and Practice of Industrial Pharmacy, 3rd edition Varghese Publishing House, Bombay, 1986, 430-456.
2. Remington AR. The Science and Practice of Pharmacy, Lippincott Williams and Wilkins, Philadelphia, 2000, 903 – 906.
3. Baveja SR, Ranga RKV, Arora J. “Examination of Natural Gums and Mucilages as Sustaining Materials in Tablet Dosage Forms”. Journal of Pharmaceutical Science, 1989, 51(4), 115-118.
4. Kakka AP, Singh M, Medirrata A. “Formulation Optimization of Diltiazem Hydrochloride Matrix Tablets Containing Modified Isphagula Husk Using Factorial Design”. Drug Development and Industrial Pharmacy, 1997, 23(11), 1055-1061.
5. Pal OP, Malviya R, Bansal V, Sharma PK. “Rosin an Important Polymer for Drug Delivery: A Short Review”. International Journal of Pharmaceutics, 2010, 3(1), 35-37.
6. Passerini N, Apertini B. “Preparation and Characterization of Ibuprofen-Poloxamer 188 Granules Obtained by Melt Granulation”. European Journal of Pharmaceutical Science, 2002, 15, 71–78.
7. Sutananta W, Carig DQM, Newton JM. “An Evaluation of the Mechanism of Drug Release from Glyceride Bases”. Journal of Pharmacy and Pharmacology, 1999, 47, 87-90.
8. Aiman A, Rana M. “Controlled Release of Tramadol Hydrochloride from Matrices Preparation using Glyceryl Behenate”. European Journal of Pharmaceutics and Biopharmaceutics, 2001, 52, 231-235.
9. Asquith M. “Pramipexole and Ropinirole: New Dopamine Agonists for Parkinson. S Disease”. Journal of the Pharmacy Society of Wisconsin, 1999, 22-28.
10. Wakode R, Bajaj A. “Formulation and Development of Once a Daily Sustained Release Matrix Tablet for Pramipexole”. Journal of Pharmaceutics and Cosmetology, 2010, 1(1), 1-9.

