ISSN: 2348-8948
Vol: 2; Issue: 8

RESEARCH PAPER

FORMULATION AND IN-VITRO EVALUATION OF PULSATILE RELEASE OF DILTIAZEM HYDROCHLORIDE

Akshay N. Jadhav, Mukesh P.Ratnaparkhi*, Mayur wattamwar, Kutmalge meghshyam

Department of Pharmaceutics, MMM's College of Pharmacy, Theragaon (Kalewadi), Pune-411033

Date Received:	Date of Accepted:	Date Published:
14-Jul-2014	26-Jul-2014	01-Aug-2014

Abstract:
Controlled drug delivery systems have acquired a center stage in the area of pharmaceutical R&D. Such systems offer temporal and spatial control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. These systems are designed according to the circadian rhythm of the body, and the drug formulation release drug rapidly and completely as a pulse after a lag time. PDDS (Pulsatile drug delivery system) system employed for treating diseases which show their intense influence at early morning, so present study is about formulating core tablet of anti-hypertensive drug with suitable superdisitegrants and then after core tablet coated with various polymer in different concentration where ethyl cellulose is common mix with other polymers. To tackle the difficulties occurs at cardiac diseases in morning such as angina attack in morning, heart attacks etc. Pulsatile release formulation develop for show their effect while such conditions at intense and patient not in condition to take medication.

Keywords: Chrono release, Time dependent, Diltiazem hydrochloride

Introduction

Chronotherapeutics is defined as a treatment system where the drug availability has been timed in accordance to circadian rhythms of drug related biological phenomena to create maximum benefit and minimizing harm. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. In chronopharmacotherapy, drug administration is synchronized with circadian rhythms. If the peak of symptoms occurs at daytime, a conventional dosage forms can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning, the timing of drug administration and nature of the drug delivery system needs careful consideration. In this case, modified-release dosage forms must be used.[1-4]

The treatment of the disease to the fullest not only depends on the medicine but it also depends on the time, release of drug at the site needed require maintaining the utilization of drug at that site. Release of drug by biological rhythm in body at specific time is proposed development of pulsatile formulation because disease active at the specific time so action of drug must show at that particular time. In this study core tablet of drug and superdisitegrants coated by water soluble as well as water insoluble polymers to increase release criteria of drug thereby tablet can achieve time at which disease level is highly intense.

These rhythms of our body rhythm are called as biological rhythm, which change with the environment. These biological clocks are also controlled by our genetic makeup. These rhythms are responsible for the changes in our body throughout the day like

blood pressure, blood coagulation, blood flow and other functions of the body. Like our body has an inbuilt 24 hour cycle in the same way some diseases will also follow the circadian patterns, chronotherapy is very useful in treating such type of diseases by adjusting the dose and the time of drug administration according to the circadian rhythms. The following is the list of some diseases which can be more significantly cured by chronotherapy.

Hypertension

Heart rate and blood pressure will be high at the time we wake up in the morning i.e. A.M and it will begin to decrease in the afternoon and it reaches to the minimum at midnight. But the blood pressure is comparatively high in case of hypertension patients upon awakening. This physiological condition is described as morning surge or A.M. surge.[5]

The systolic blood pressure rises up to 3mmHg/hour for 4-6 hours after getting up called post-awakening and the diastolic blood pressure also rises up to 2mmHg/hour.

Myocardial Infarction

The release of the catecholamine's, cortisol, increase in platelet aggregation and the vascular tone will be high in the morning. These are the main reasons for the outburst of the myocardial infraction in the morning with 34% events taking place from 6 A.M till noon. Acute cardiac arrest and transient. myocardial ischemia takes the lead as well in the morning. Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slowchannel blocker). Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform and has a molecular weight of 450.98. The therapeutic effects of diltiazem hydrochloride are believed to be related to its ability to inhibit the cellular influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

MATERIALS AND METHODS

MATERIALS

Diltiazem HCL was obtained as a gift sample from wokhadt Ltd. (Mumbai, India). cyclodextrin
Was obtained as gift sample from research fine chemical lab. mumbai Crosspovidone, NA-cmc, Xanthan gum also gifted as sample by research fine chemical lab. mumbai. Ethyl cellulose was gifted by Colcorcon Asia Pvt. Ltd. (Goa, India). All other excipients used were of analytical grade.

METHODS

Cup method

Preparation of core tablet by direct compression

Core tablets of Diltiazem hydrochloride were prepared by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 mins. Blended drug/polymer mixture of the formulations were subjected for precompressional evaluation such as bulk and tapped density, compressibility index , Hausner's ratio and angle of repose Tablets were compressed in Minipress Tablet Compression Machine using 8 mm round concave punches. The composition of core tablet is given in Table 1.

Preparation of press coated tablet

A **RSM** was used in this study. In this design 2 factors were evaluated, each at 2 levels, and experimental trials were performed at all 15 possible combinations. Polyox, Na-Cmc, Xanthan gum, ethyl cellulose. Coating layer were selected as independent variables. The times required for maintaining lag time (Y) were selected as dependent variables. Na-CMC, Xanthan gum and polyethylene oxide are in different concentrations, ethyl cellulose is fixed in coating tablet. The experimental design with corresponding formulation outline in Table no.2

RESULT AND DISCUSSION

FTIR Spectrophotometer of drug

The IR spectrum of the pure drug Diltiazem shows in figure 1

Precompression Parameters of Core Tablet Powder Blend

Bulk Density & Tapped Density

Bulk density & tapped density were evaluated which were found as near about 0.51 g/cm^3.

Angle of repose

The powder blends indicated good flowability with the angle of repose values ranging from 25 to 33° according to fixed funnel method.

Carrs index & Hausners ratio

The result of compressibility index was between 9 to 15, which indicates good to fair flow properties & for Hausners ratio was near/less about 1.22, which indicates free flowing powder.

Postcompression Parameters of Press-Coated Tablets

Hardness

The hardness of all the tablets was between 8 and 9kg/cm^2.

Friability

In the present study, the loss in total weight in friability test was in the range of 0.70 to 0.94% that indicates, the percentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits.

Table no.1 Composition of Core Tablet

	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG(mg)	10	10	10	10	10	10	10	10	10
CP(mg)	5	7.5	10	-	-	-	-	-	-
SSG(mg)	-	-	-	5	7.5	10	-	-	-
CCS(mg)	-	-	-	-	-	-	5	7.5	10
MC(mg)	84	81.5	79	84	81.5	79	84	81.5	79
MS(mg)	1%	1%	1%	1%	1%	1%	1%	1%	1%

Total weight of core tablet 100 mg
SSG-Sodium starch glycolate, CP- Crospovidone, CCS- Crosscarmellose sodium,
MC- Microcrystalline cellulose and MS-Microcrystalline cellulose

Table no.2 composition of coating Tablet

Run	Ratio	Polymers
1	60:00	NA-CMC+EC
2	100:00	XANTHAN+EC
3	50:00	NA-CMC+EC
4	53:75	XANTHAN+EC
5	100:00	POLYOX+EC
6	75:00	XANTHAN+EC
7	90:00	NA-CMC+EC
8	50:00	POLYOX+EC
9	100:00	NA-CMC+EC
10	60:00	POLYOX+EC
11	90:00	POLYOX+EC
12	80:00	XANTHAN+EC
13	80:00	POLYOX+EC
14	50:00	XANTHAN+EC
15	80:00	NA-CMC+EC

Total weight of coated tablet 300mg, 00 is quantity of EC (Ethyl cellulose)

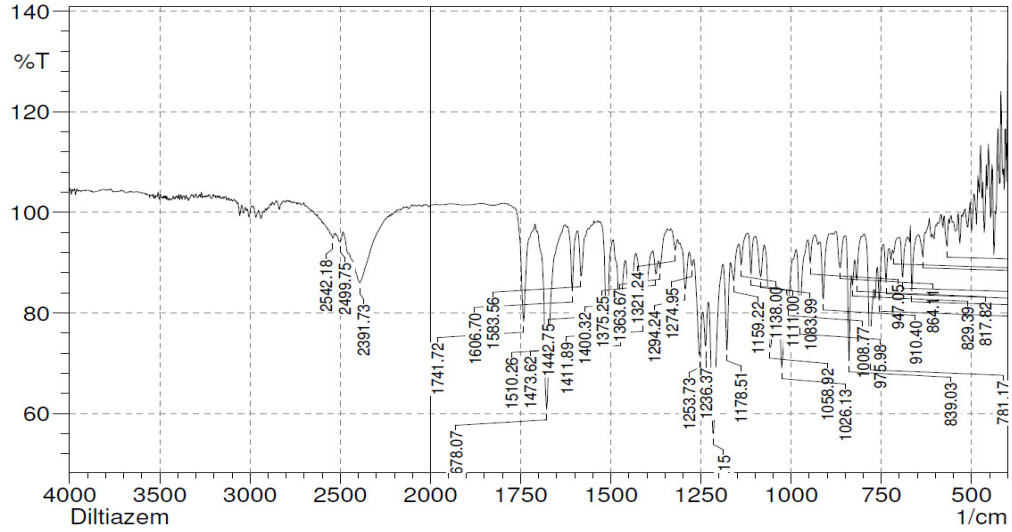

Figure No 1: IR spectrum of the Diltiazem Drug

Compatability studies

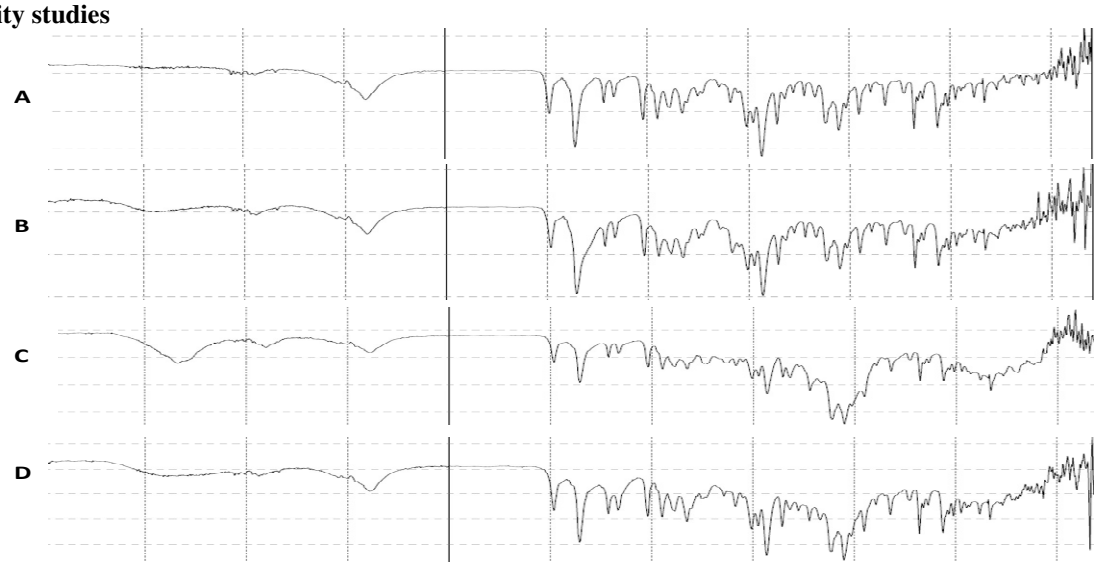

Fig. No.2: IR spectrum of Diltiazem and excipients A) Drug B) Drug+ Crosspovidone C) Drug+MCC D) Drug+ Magnesium stearate

Table 3 Pre-Compression Parameter For Powder Blend of Core Tablet

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density(g/cm^3)	0.50	0.454	0.454	0.50	0.50	0.454	0.50	0.454	0.454
Tapped Density(g/cm^3)	0.555	0.555	0.555	0.625	0.625	0.555	0.555	0.625	0.555
Angle of Repose(θ)	29.33	29.33	25.17	30.48	31.52	33.13	33.65	27.87	25.34
Carrs index (%)	9.90	13.12	11.04	14.33	12.67	10.25	9.9	15.03	10.36
Hausners ratio (HR)	1.11	1.15	1.22	1.20	1.25	1.22	1.11	1.37	1.22

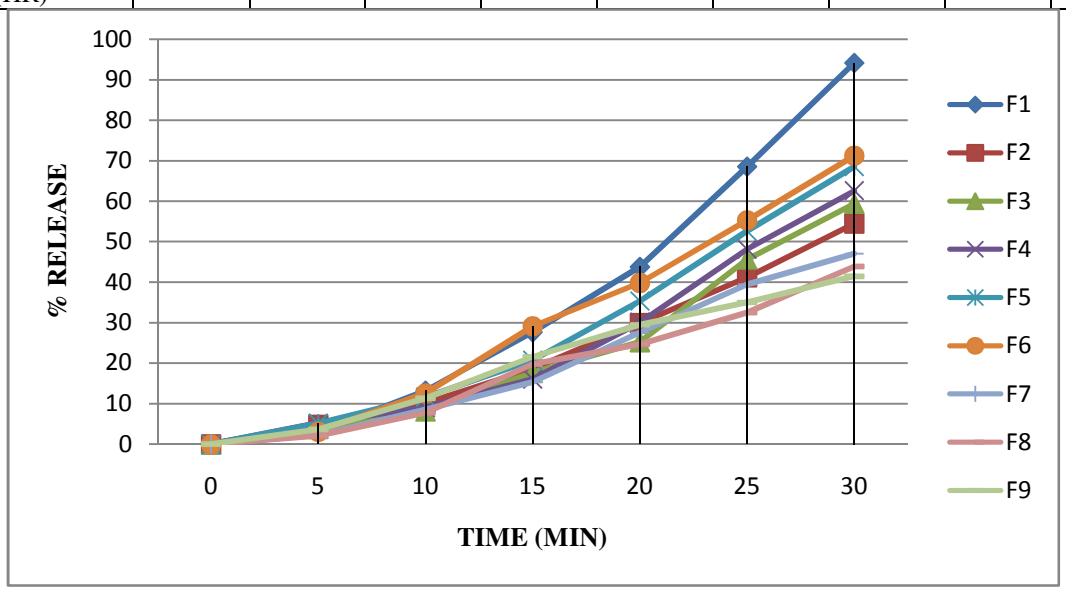

Fig no.3:- % Drug Release Of Core Tablet

Table no 4. Post compression Parameter of coated tablet of F1 to F9

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (Kg/cm^2) (n=3)	8±0.45	8.5±0.32	9±0.23	9±0.21	8±0.41	8.5±0.19	8±0.64	8±0.80	9±0.80
Thickness(mm) (n=3)	6.02±0.15	6.13±0.17	5.95±0.26	5.97±0.15	6.09±0.27	5.93±0.26	5.89±0.15	6.17±0.027	6.10±0.7
Diameter(mm)(n=3)	10.01±0.01	10.00±0.02	10.00±0.02	10.01±0.01	10.02±0.02	10.01±0.02	10.00±0.02	10.01±0.01	10.01±0.02
Weight Variation(%) (n=20)	290±1.29	300±1.13	298±1.24	300±0.80	290±0.73	278±1.17	260±0.61	272±0.62	295±0.75
Friability(%) (n=10)	0.85	0.94	0.70	0.72	0.77	0.76	0.88	0.92	0.83

Table no 5. Post compression Parameter of coated tablet of F10 to F15

	F10	F11	F12	F13	F14	F15
Hardness (kg/cm^2) (n=3)	9±0.31	8±0.39	8.5±0.21	9±0.70	8.5±0.31	9±0.19
Thickness (mm) (n=3)	6.01±0.17	6.17±0.15	5.98±0.21	6.02±0.15	6.07±0.37	5.96±0.28
Diameter (mm) (=3)	10.00±0.02	10.02±0.02	10.01±0.02	10.02±0.01	10.01±0.02	10.02±0.01
Weight variation (%)	298±1.09	294±1.29	301±0.82	292±0.78	282±1.119	300±1.12
Friability (%) (n=10)	0.91	0.73	0.75	0.80	0.79	0.88

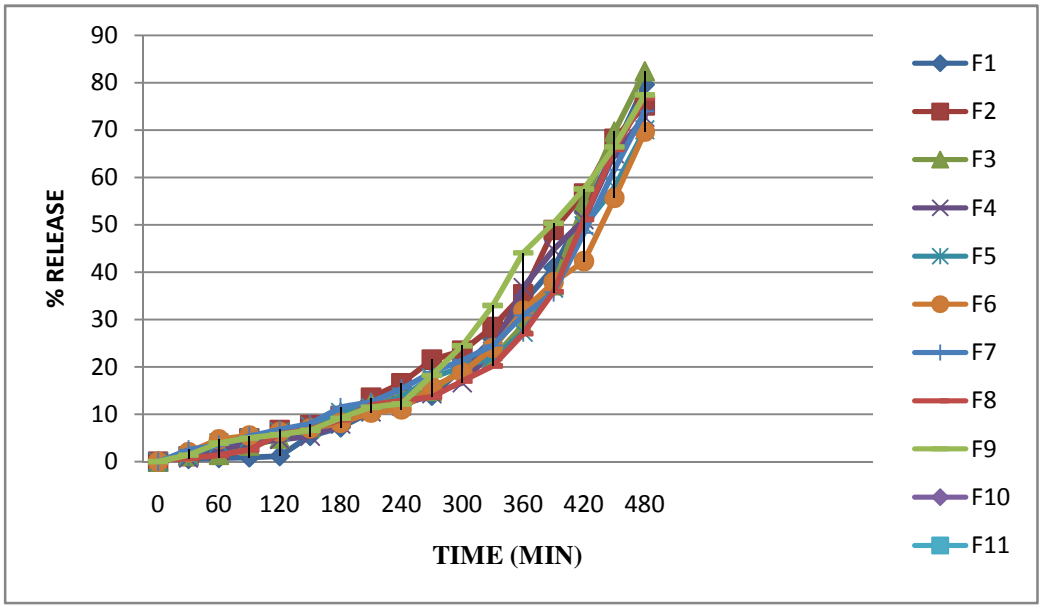

Fig. no. 16 % Drug Release of coated formulations

Weight variation test

In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within limit, and hence all formulations passed the test for uniformity of weight as per official requirement

In vitro drug release study of tablets

In-vitro dissolution testing is important in the development of solid doage forms. It provides decisive information on formulation selection, the critical processing variables. In order to provide this information, dissolution testing should be conducted in physiochemical and hydrodynamically defined conditions to simulate the environment that the dosage form encounters in the GI tract. Conventional dissolution testing proposed in USP appears unable to discriminate drug mechanisms. For in-vitro evaluation of Pulsatile drug delivery systems, the ideal dissolution testing should closely mimic the in-vivo conditions with regard to pH, bacteria, types of enzymes, enzymatic activity, fluid volume and mixing intensity. Apparently, such dissolution specifications will be very difficult, if possible at all, to be standardized and validated. Dissolution testing of Pulsatile delivery systems with the conventional paddle method at 50 rpm and 37+0.5^{o}c has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the Pulsatile delivery system might encounter in-vivo The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in pH 1.2 buffer for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analysed by UV spectrophotometer for the presence of the drug. Dissolution tests were performed in triplicate.

CONCLUSION

Pulsatile delivery formulation were prepared by direct compression press coating using 2^3 full factorial design with polymers as Ratio of Polyox, NA-CMC, Xanthan gum and ethyl cellulose. Polyox having a property of fast hydration & swelling useful for maintaining lag time. Xanthan gum having more viscosity when come in contact with solvent. Ethyl cellulose is hydrophobic polymer used to inceased lag time.

Tablets were evaluated for thickness, hardness, %friability, uniformity of weight, uniformity of content and dissolution studies. All the formulations were shown the drug release but Formulation F1 was considered as optimized containing NA-CMC and ethyl cellulose in ratio 60:00 drug released upto 4 hrs.

ACKNOWLEDGEMENT

Authors are thankful to Principal Marathwada Mitra Mandals College of Pharmacy, Kalewadi (Thergaon), Pune for providing all ingredients and required infrastructure for the conduct of this research work.

REFERENCES

1. Dr. Abhijit V. Gothoskar, Anagha M. Joshi, Nitin H. Joshi; "Pulsatile Drug Delivery Systems: A Review", Articles –Archives Drug Delivery Technology, Issue Date: Vol. 4 No. 5 June 2004, Posted On: 3/28/2008.
2. Sachin Survase, Neeraj Kumar; "Pulsatile Drug Delivery: Current Scenario", CRIPS Vol. 8 No. 2 April-June 2007, page no. 27-33.
3. Till Bussemer, Roland A. Bodmeier; "Drug Delivery: Pulsatile Systems", Encyclopedia of Pharmaceutical Technology, Third Edition, Volume 1 published by Informa Healthcare USA Inc., page no. 1287-1297.
4. Bhupendra. G. Prajapati, Himanshu Solanki; "Recent Techniques for Oral Time Controlled Pulsatile Technology", The Internet Journal of Third World Medicine. 2009 Volume 8 Number 1.
5. Eiji Fukui, Katsuji Uemura, Masao Kobayashi; "Studies on applicability of press coated tablets using hydroxypropyl cellulose (HPC) in the outer shell for timed release preparations" Journal of Controlled Release, Volume 68 (2000), page no. 215–223
6. Shan Yang Lin, Kung Hsu Lin, Mei Jane Li; "Micronized ethyl cellulose used for designing a directly compressed time-controlled disintegration tablet", Journal of Controlled Release, Volume 70 (2001), page no. 321–328.
7. Madhusudan Hariharan, Vishal K. Gupta; "A Novel Compression Coated Tablet Dosage Form", Pharmaceutical Technology, YEARBOOK 2001, page no. 14–19.
8. Yoshiteru Watanabe, Baku Mukai, Ken-ichi Kawamura, Tatsuya Ishikawa, Michihiro Namiki, Naoki Utoguchi, and Makiko Fujii; "Preparation and Evaluation of Press-coated Aminophylline Tablet Using Crystalline Cellulose and Polyethylene Glycol in the Outer Shell for Timed Release Dosage Forms", YAKUGAKU ZASSHI Volume 122(2), 2002, The Pharmaceutical Society of Japan, page no.157–162.
9. Srisagul Sungthongjeena, Satit Puttipipatkhachorna, Ornlaksana Paeratakulc, Andrei Dashevskyb, Roland Bodmeier; "Development of pulsatile release tablets with swelling and rupturable layers", Journal of Controlled Release, 95 (2004), page no.147– 159.
10. J. Qureshi, Mohd. Amir, Alka Ahuja, Sanjula Baboota, J. Ali; "Chronomodulated drug delivery system of salbutamol sulphate for the treatment of

nocturnal asthma", Indian Journal of Pharmaceutical sciences, Volume 70, Issue 3, 2008, Page no. 351–356.

11. Qureshi J., Ahuja A., Baboota S., Chutani K., Jain S., Ali J.; "Development and evaluation of a time-specific pulsatile-release tablet of Aceclofenac: A solution for morning pain in rheumatoid arthritis", Methods and Findings Experimental Clinical Pharmacology, 2009, 31(1) 15.
12. Janugade B. U., Patil S. S., Patil S. V., Lade P. D.; "Formulation and evaluation of press-coated Montelukast sodium tablets for pulsatile Drug delivery system", International Journal of Chem. Tech Research, Volume 1, No.3, July – September 2009, page no. 690–695.
13. Toyohiro Sawada, Hiromu Kondo, Hiroshi Nakashima, Kazuhiro Sako, Masahiro Hayashi; "Time-release compression coated core tablet containing nifedipine for chronopharmacotherapy", International Journal of Pharmaceutics, 280 (2004) page no.103–111.
14. Ashish Babulal Rane, Surendra Ganeshlal Gattani, Vinayak Dinkar Kadam, Avinash Ramrao Tekade; "Formulation and Evaluation of Press Coated Tablets for Pulsatile Drug Delivery Using Hydrophilic and Hydrophobic Polymers", *Chem. Pharm. Bull.,* Vol.57, No.11 ,(2009) page no.1213—1217.