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Formulation and Evaluation of Nicardipine Bilayered Tablets

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ABSTRACT

Nicardipine is a medication used to treat high blood pressure and angina. It belongs to the dihydropyridine class of calcium channel blockers. It is also used for Raynaud's phenomenon. It is available in by mouth and intravenous formulations. It has been used in percutaneous coronary intervention. It has a plasma half-life about (8.6 h) and bioavailability is 15-45% orally. The present work aims to develop a stable and optimized bilayer dosage form containing immediate release and extended release drug Nicardipine as extended release dosage form.For the formulation of Bilayered tablets polymers such as Ethyl cellulose, Sodium CMC, CCS, SSG, Magnesium stearate, Talc, PVP K30 and MCC. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. Preformulation studies were carried out to optimize the ratios required for various Ethyl cellulose, Sodium CMC, CCS, SSG, Magnesium stearate, Talc, PVP K30 and MCC. Based on various evaluation parameters formulation M6 (IR) &M6F3 (SR) was selected as optimized formulation. It was observed that Formulations M6 (IR) & M6F3 (SR) gave maximum drug release within time. All formulations were subjected for drug release kinetics studies viz. Zero order, First order, Higuchi matrix, Peppas model equations and the formulations of sustained release (SR) formulations followed zero order release with non-fickian diffusion mechanism. Thus conclusion can be made that stable dosage form can be developed for Nicardipine as immediate release & Sustain release by Bilayered tablets.

Key words : Nicardipine SSG, CCS, Soidum CMC, Ethyl cellulose, Magnesium stearate, Talc, PVP K30 and MCC**.**

Introduction

There are many ways to deliver drugs into the body like oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through skin), pulmonary (through inhalation) etc [1-6].

Tablets ("Pharmaceutical powder compacts") are the most common, convenient and preferred means of the existing administration methods for the systemic delivery of drugs. It provides, ease of dose administration, patient compliance and flexibility in formulations. The effective oral drug delivery practice depends upon various factors like gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Conventional dosage form produce wide range of fluctuation in drug concentration in the blood stream and tissues with undesirable toxicity and poor efficiency. Factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery[7-11].

The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased.

The main objective of combination therapy is to encourage the utilization of lower doses of drugs to treat patients and also to minimize dose dependent side effect and adverse reactions. To overcome the drawbacks of single layer combination tablet this concept was came into force. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).[12-14]

MATERIALS AND METHODS

Nicardipine were obtained from BMR Chemicals, Hyderaded. Sodium CMC, Ethyl Cellulose, Poly vinyl pyrrolidone K 30, Crosspovidone XL, Cross carmellose sodium, Sodium Starch Glycolate were obtained from Narmada Chemicals, Hyderaded.

Preparation of Bilayer tablets

a) Preparation of Immediate release layer:

The Immediate release layer contains uniform mixture of Nicardipine, Sodium starch glycolate, & CCS were weighed followed by shifting through 40# sieve and mixed well for 10min. finally prepared powder lubricated with magnesium stearate and Talc the well mixed powder were used as upper layer.

b) Preparation of Sustained release layer:

25mg of Nicardipine, Sodium CMC & ethyl cellulose ,variable amount using of MCC, PVP K30, Magnesium stearate and Talc was mixed properly in a mortar with weighed amount of polymers and excipients, The well-mixed powder was compressed by direct compression technique and used as sustained release layer.

c) Preparation of Bilayer tablet:

Bilayer tablets were prepared by combining of immediate release layer and various formulations of sustained release layer. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured into the die, containing initially compressed matrix tablet on multi station punching machine using flat punches, with the hardness of 6-8 kg/cm2.

FORMULATION DESIGN

Formulation of Immediate release layer (Nicardipine).

Ingredients (mg)	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Nicardipine	25	25	25	25	25	25
SSG	3	6	9	-	-	-
Croscarmellose sodium	--	--	--	3	6	9
MCC	56	53	50	56	53	50
Manitol	10	10	10	10	10	10
Mg stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total wt	100	100	100	100	100	100

Formulation of Bilayer tablets of Nicardipine

Ingredients (mg)	**M6F1**	**M6F2**	**M6F3**	**M6F4**	**M6F5**	**M6F6**
IR formulation (M6)	100	100	100	100	100	100
Nicardipine	25	25	25	25	25	25
Ethyl cellulose	15	30	45	--	--	--
Sodium CMC	--	--	--	15	30	45
PVP K30	25	25	25	25	25	25
MCC	75	60	45	75	60	45
Talc	5	5	5	5	5	5
Mg.Sterate	5	5	5	5	5	5
Total tablet weight	250	250	250	250	250	250

***In vitro* Dissolution Studies:**

Dissolution for Immediate release tablets of Nicardipine

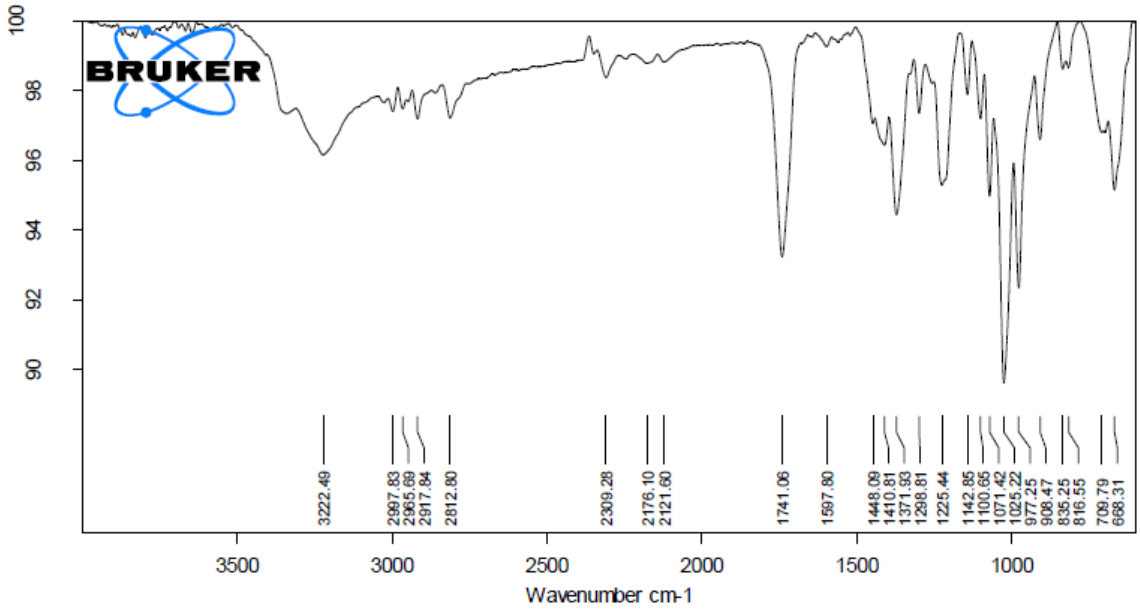
The release rate of Nicardipine from immediate release tablets was determined using USP dissolution testing apparatus II (paddle). The dissolution test was performed using 900ml of 6.8pH phosphate buffer solution at 37.5± 0.5ºC and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at times 5, 10, 15, 20, 30, 40, 50, & 60 mins and the samples were replaced with fresh dissolution medium. The samples were observed for absorbance at wavelength of 235 nm.

In vitro drug release studies of bilayer tablets:

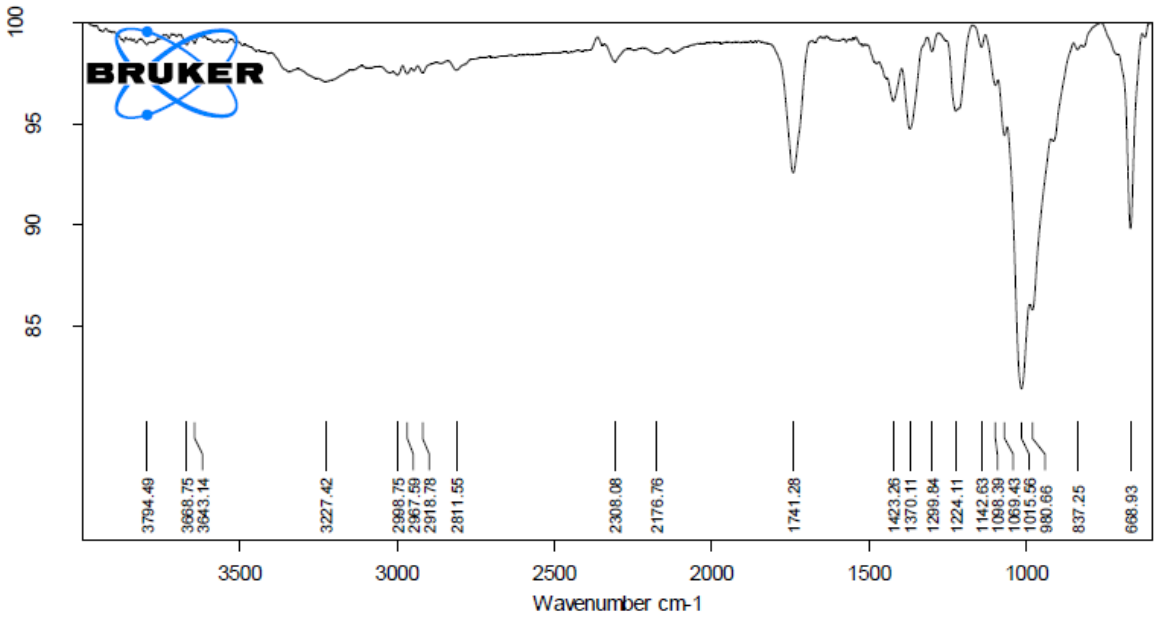
In vitro drug release studies of bilayer tablets were carried out using USP dissolution apparatus type II in 900mL of 0.1N HCl buffer up to 12 hours. Samples were collected at regular intervals of time and filtered. The collected samples were filtered and observed in UV spectrophotometer.

FT-IR SPECTROSCOPY STUDY.

In the present study FT-IR data of drug and excipient was compared with standard spectrum of pure drug. The characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymer carrier formulation were noted. The IR spectra showed that there is no significant evidence for interaction between the drug and the excipients. The figure shows the IR spectrum of pure Nicardipine, ethyl cellulose, Sodium CMC, SSG, and Crospovidone, Nicardipine best formulations respectively



IR spectra of Nicardipine pure



IR spectra of Nicardipine + Excipeints

Discussion: The IR spectrum of pure drug was found to be similar to the standard spectrum of Nicardipine.

From the spectra of Nicardipine, combination of Nicardipine with polymers, it was observed that all characteristic peaks of Nicardipine were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and excipients.

Characterization of blend (immediate release)

Pre Compression parameters (Immediate release)

Code	Angle of Repose ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio ±SD
M1	22.16±0.15	0.376±0.027	0.425±0.035	14.35±0.32	1.19±0.032
M2	24.75±0.65	0.345±0.059	0.431±0.016	15.41±0.15	1.17±0.026
M3	24.55±0.47	0.384±0.026	0.422±0.025	11.28±0.54	1.14±0.025
M4	23.60±0.49	0.391±0.014	0.439±0.010	14.14±0.56	1.15±0.044
M5	22.79±0.59	0.376±0.025	0.419±0.048	12.52±0.25	1.18±0.026
M6	22.56±0.47	0.384±0.056	0.428±0.064	14.77±0.14	1.16±0.035

Inference:

The angle of repose of different formulations (M1-M6) was found to be in the range of 22.16±0.15 to 24.75±0.65 which indicates that material had excellent flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.345±0.059 to 0.391±0.014. Tapped density was found between 0.419±0.025 to 0.439±0.010. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.28±0.54 - 15.41±0.15 and Hausner's ratio from 1.14±0.025 - 1.18±0.026 which reveals that the blends have good flow character.

Characterization of Immediare Release Tablets

Post Compression parameters

Formulation code	Mean Hardness Kg/cm^2	Thickness	Diameter (mm)	Average weight (mg)	Friability % w/w	Disintegration test (sec)	Mean drug content %
M1	3.5±0.02	2.67±0.06	8.72±0.16	98.80±0.42	0.72±0.15	115±1	97.65±0.32
M2	3.7±0.04	2.81±0.04	8.86±0.02	95.45±0.63	0.52±0.26	97±2	98.85±0.45
M3	3.6±0.26	2.56±0.04	8.46±0.01	98.82±0.52	0.68±0.34	64±3	97.05±0.85
M4	4.0±0.31	2.91±0.16	8.73±0.06	94.46±0.19	0.84±0.58	97±27	98.46±0.69
M5	4.2±0.05	2.24±0.17	8.94±0.07	99.73±0.42	0.97±0.96	57±4	97.58±0.42
M6	3.8±0.01	2.65±0.05	8.52±0.09	98.76±0.01	0.64±0.21	75±2	99.84±0.15

Inference:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.5 – 4.2 kg/cm^2.

All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±10% of the tablet weight.

Friability values were found to be less than 1% in all the formulations M1 – M6 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

The % drug content for all the formulations were close to 100 and varied between 97.05 to 99.84 %.

Pre Compression parameters

Formulation code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
M6F1	32.66±1.01	0.68±0.41	0.67±0.12	14.07±0.63	1.17±0.37
M6F2	31.95±1.15	0.56±0.52	0.65±0.52	13.70±0.14	1.14±0.26
M6F3	30.87±0.62	0.62±0.65	0.69±0.14	11.30±0.62	1.13±0.56
M6F4	29.75±0.45	0.60±0.45	0.64±0.36	10.95±0.23	1.15±0.26
M6F5	31.92±0.75	0.59±0.35	0.67±0.42	11.57±0.26	1.16±0.14
M6F6	32.41±0.65	0.58±0.15	0.68±0.74	12.64±0.52	1.14±0.13

Inference:

The angle of repose of different formulations was ≤ 32.66 which indicates that material had good flow property. So it was confirmed that the flow property of bends were free flowing.

The bulk density of blend was found between 0.56g/cm^3 to 0.62 g/cm^3.Tapped density was found between 0.64g/cm^3 to 0.69g/cm^3.These values indicate that the blends had good flow property.

Carr's index for all the formulations was found to be between 10.95-14.07 and Hausner's ratio from 1.13-1.17 which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content

Table : Characterization of Bilayer tablets

Formulation	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Drug content (%)
M6F1	248.50±0.41	3.11±0.09	10.90±0.06	6-8	0.57±0.01	95.63±0.15
M6F2	234.00±0.65	3.18±0.01	10.93±0.04	6-8	0.69±0.06	98.64±0.25
M6F3	246.57±0.53	3.21±0.01	10.93±0.13	6-8	0.42±0.01	97.42±0.36
M6F4	249.73±0.42	3.22±0.13	10.64±0.02	6-8	0.15±0.12	99.25±0.42
M6F5	251.00±0.16	3.30±0.06	10.93±0.16	6-8	0.56±0.03	96.46±0.15
M6F6	247.63±0.03	3.33±0.04	10.91±0.08	6-8	0.38±0.05	97.06±0.0

Inference:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 6 - 8 kg/cm^2.

All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the tablet weight.

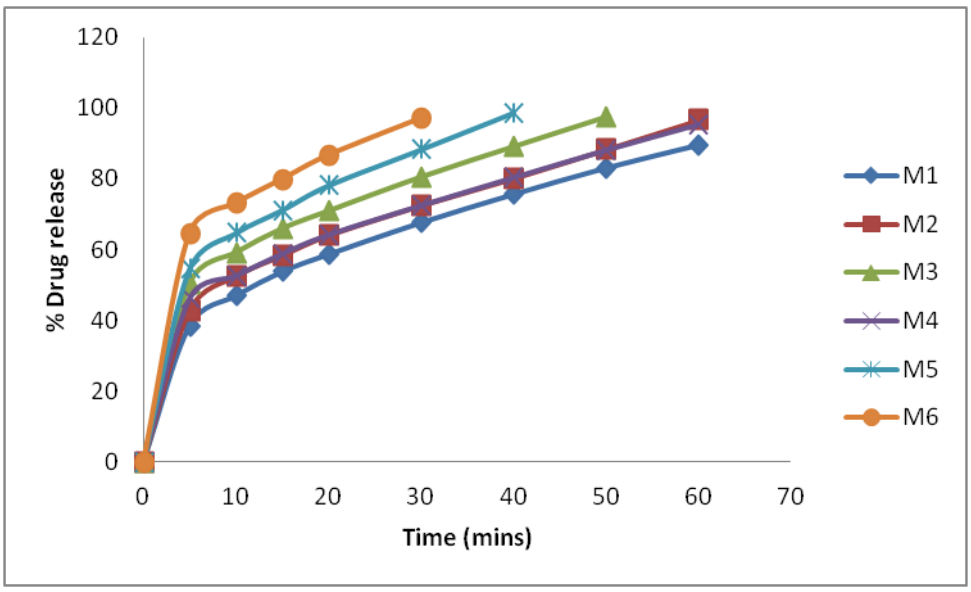
Friability values were found to be less than 1% in all the formulations M6F1 – M6F6 were considered to be satisfactory ensuring that all the formulations are mechanically stable.

The % drug content for all the formulations were close to 100 and varied between 95.63to 99.25%.

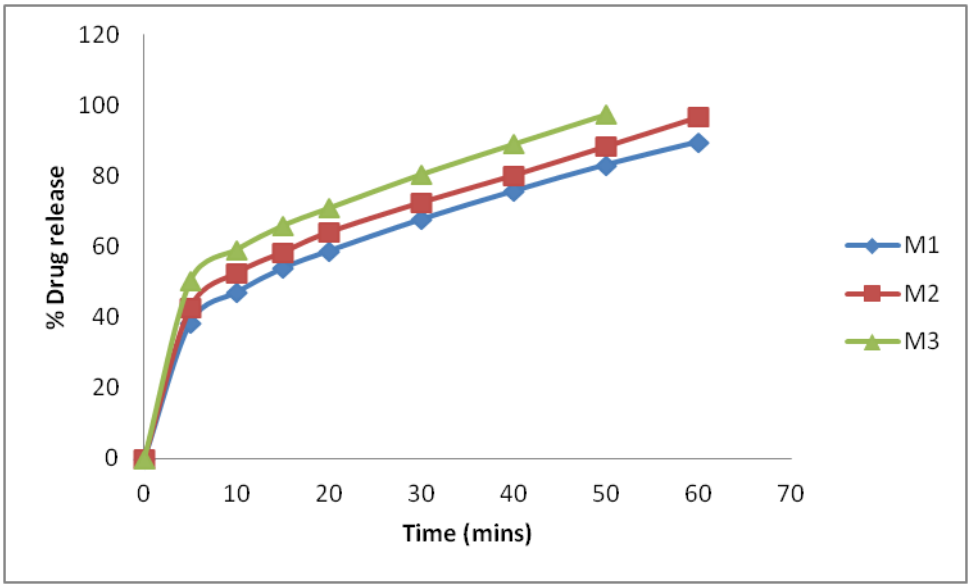
In vitro dissolution studies:

Percent Drug Release of Nicardipine (IR) Tablets for all formulations (M1-M6)

Time (min)	M1	M2	M3	M4	M5	M6
0	0	0	0	0	0	0
5	38.53	42.86	50.49	46.19	54.52	64.61
10	47.06	52.56	59.21	52.63	64.69	73.08
15	53.86	58.43	65. 96	58.84	71.19	79.85
20	58.76	64.08	70.94	64.19	78.16	86.59
30	67.72	72.52	80.49	72.48	88.36	97.02
40	75.73	80.19	89.05	80.35	98.75	
50	83.19	88.36	97.43	88.09		
60	89.67	96.63		95.35		



Percent Drug Release versus Time Plots of Nicardipine Tablets M1-M6



Percent Drug Release versus Time Plots of Nicardipine Tablets for M1-M3

Discussion:

The in vitro drug release profiles of immediate release tablets of Nicardipine formulated by using SSG as a super disintegrant in three different ratios in different formulations like M1 with 3mg shows maximum drug release at the end of 60mins i.e., 89.67 %. While formulation M2 containing SSG 6mg as superdisintegrant shows 96.63% of drug release at the end of 60mins. While formulation M3 containing SSG 9mg as superdisintegrant shows 97.43% of drug release at the end of 50mins.

By observing the dissolution profiles of M1-M3 increase in the superdisintegrant concentration shows decrease in the drug release time. So to Know the best disintegrant concentration further trails were formulated by using CCS as a super disintegrant.

Conclusion

The study involves preformulation studies, formulation, evaluation and stability studies of prepared matrix tablets. The physical evaluation of API along with excipients has shown compatibility supporting the choice of excipients. FTIR studies reveal no incompatibility between drug, polymer and various excipients used in the formulations.CRDDS of a model drug were formulated and evaluated with different polymers. Formulations with Ethyl cellulose (18%) polymers has successfully releases the model drug release upto 12hours and they were formulated by using direct compression.Immediate release

tablets of a model drug were formulated and evaluated with different polymers. Formulations with CCS polymers has successfully releases the model drug release within time and they were formulated by using direct compression.The dissolution profiles and kinetic studies (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) indicate that the release of Nicardipine follows zero order release and with non-fickian diffusion mechanism.

REFERENCES

1. W. Chien, Fundamentals of controlled-release of drug administration in: J. Swarbrick (Ed.), Novel Drug Delivery System Marcel Dekker, New York, 1982, pp. 465–574.
2. Buri, F. Puisicux, E. Doelker, J.P. Benoit, Formes Pharma centiques Nouvelles, Ed. Technique et Documentation, Lavoisier, Paris, 1985.
3. R. Wilding, A.J. Coupe, S.S. Davis, The role of gamma scintigraphy in oral drug delivery, Adv. Drug Deliv. Rev. 1991; 7: 87– 117.
4. Lee. Diffusion-controlled matrix systems, in: A. Kydonieus (Ed.), Treatise on Controlled Drug Delivery, Marcel Dekker, New York, 1992, pp. 155–198.
5. A. Peppas. Hydrogels in Medicine and Pharmacy, vols. I, II and III, CRC Press, Boca Raton, FL, 1988.
6. The Extra Pharmacopoeia, 31st Ed. The Pharmaceutical Press, London1996, pp. 936–937.
7. Martin, P. Bustamante and A. Chun, Micromeritics, in Physical Pharmacy-Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lippincott Williams and Wilkins, Baltimore 2002, pp. 446–448.
8. Bogan, R.K. Treatment options for insomnia—pharmacodynamics of zolpidem extended-release to benefit next-day performance. Postgrad. Med. 2008; 120: 161–171.
9. Dey S and Chatto PS. Formulation and evaluation of fixed dose combination of bilayer gastro retentive matrix tablet containing atorvastatin as fast release and atenolol as sustained release. BiomedRes Inter. 2014;10(1155):396106.
10. Banu H and Sahariar MR. Formulation development of bi-layer acetaminophen tablets for extended drug release.J Chem Pharm Res.2011;3(6):348-360.
11. Solanki PD. Formulation evaluation and optimization of bilayer floating tablet of repaglinide and glipizide. Inter J Pharm Rese Schoc.2012;1(3):123-134.
12. Sadhana RS and Vidya MM. Development and evaluation of bilayer floating tablets of diltiazemhcl. Inter J Pharm Pharm Scien.2014;6(2):62-65.
13. Sharma V, Nagpal M, Jain UK, Mangotia A and Kumar R. Antidiabetic drug and combination therapy. ARPB. 2013;3(2):389-394.
14. Ali SH and Reddy BR. Formulation and evaluation of bilayer tablet of atorvastatin and pioglitazone for metabolic disorder. IAJPS. 2014;1(6):448-455.