WORLD JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

www.wjcmpr.com ISSN: 2582-0222

Formulation development and in vitro evaluation of bilayer tablets nicardipine

P.Vamsikrishna*[1], T.Malyadri[2] , Ch.Saibabu[3]

[1]Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

[2]Assistant professor, Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

[3]Head, Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101

Abstract

The present work aims to develop a stable and optimized bilayer dosage form containing immediate release &extended release drug Nicardapine as an extended-release dosage form. A potent calcium channel blocker with marked vasodilator action. It has antihypertensive properties and is effective in the treatment of angina and coronary spasms without showing cardio depressant effects. It has also been used in the treatment of asthma and enhances the action of specific antineoplastic agents. It has a plasma half-life of about (8.6h) and bioavailability is 15-45% orally. For the formulation of Bilayered tablets polymers such as Ethylcellulose, 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 Ethylcellulose, Sodium CMC, CCS, SSG, MCC, and PVP-K30. Based on various evaluation parameters formulation M6 (IR) & M6F3 (SR) were 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, Peppasmodel equations, and the formulations of floating sustained-release formulations followed the zero-order release with non-fickian diffusion mechanism. Thus conclusion can be made that a stable dosage form can be developed for Nicardapine as immediate release & sustained release by Bilayered tablets.

Article History:
Received on: 17.04.2021
Revised on: 22.05.2021
Accepted on: 31.05.2021

Key words:
Nicardapine, CCS, SSG, FTIR, Ethyl cellulose, Sodium CMC.

*Corresponding Author
Name: P.Vamsikrishna
Email: malyapharma22@gmail.com

DOI: https://doi.org/10.37022/wjcmpr.vi.172

This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Copyright © 2021 Author(s) retain the copyright of this article.

Introduction

An ideal drug delivery system should be able to show either spatial (or) temporal delivery of drugs. Spatial delivery relates to targeting a drug to a specified organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed extended release dosage form shows spatial or temporal delivery of drugs. One of the oral drug delivery system which meant to prolong the residence time of dosage form in the stomach is Gastro - retentive drug delivery system (GRDDS). The successful Received on development of gastro-retentive drug delivery systems requires an understanding of two aspects of the system, namely: The physiochemical characteristics of the drug and Anatomy and physiology of GIT and Characteristics of Dosage forms [1]. Gastro-retentive drug delivery systems (GRDDS) or Hydro-dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Prolonged gastric retention improves oral bioavailability of drug reduces drug wastage, and improves solubility for drugs that are less soluble in a high pH environment. GRDDS has applications for local drug delivery to the stomach and proximal small intestines. Thus Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [2]. Various attempts have been made to retain the dosage form in the stomach as a way of increasing the gastric retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric- emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the

surface of the meal [3]. The term bilayered tablets refers to tablet containing subunits that may either be the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics. These tablets are composed of two layers of granulation compressed together. They have appearance of a sandwich because the edges of each layer are exposed.. Bilayer Floating tablets are prepared with one layer of drug for immediate release which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach [4]. Nicardipine [5] is a potent calcium channel blocker with marked vasodilator action. It has antihypertensive properties and is effective in the treatment of angina and coronary spasms without showing cardiodepressant effects. It has also been used in the treatment of asthma and enhances the action of specific antineoplastic agents.

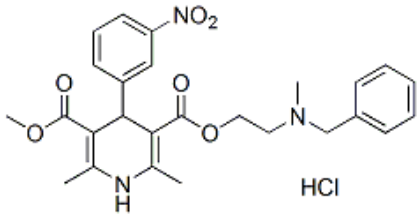

Fig 01: Chemical structure of Nicardipine

Materials

Nicardipine and Ethyl Cellulosefrom BMR Chemicals, Hyd , Sodium Starch Glycolate , Croscarmellose sodium**,** Sodium CMC from Narmada Chemicals, Hyd, Magnesium Stearate,MCC, Poly vinyl pyrrolidone K 30,talc from SD Fine chemicals, Mannitol from Agastan Bio Cheme Pvt Ltd

Methodology

Preformulation studies [6]

Solubility studies

Nicardipine

Solubility of Nicardipine was determined in water, 0.1 N HCl, pH 6.8 and Ph 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Nicardipine in different beakers containing different solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 248nm by using UV Spectrophotometry.

Drug-Excipient Compatibility Studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information.

FT-IR Studies

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal(absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

Determination of UV spectrum of Nicardipine

10mg of Nicardipine was dissolved in 10ml of buffers so as to get a stock solution of 1000 µg/ml concentration. From this 1ml solution was withdrawn and diluted to 10ml to get a concentration of 100µg/ml (SS-II). From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of standard calibration curve of Nicardipine in 0.1N HCl

Procedure

Preparation of standard solution

Standard stock solution of Nicardipine was prepared in 0.1N HCl. 10 mg of Nicardipine was accurately weighed into10ml volumetric flask and dissolved in small quantity of 0.1N HCl. The volume was made up with 0.1N HCl to get a concentration of 1000µg/ml (SS-I) From this 1ml solution was withdrawn and diluted to 10ml to get a concentration of 100µg/ml(SS-II).

Preparation of working standard solutions

Further,from (SS-II) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml and 1.2ml were pipette into 10ml volumetric flasks. The volume was made up with 0.1N HCl to get the final concentrations of 2, 4, 6, 8, 10 and 12 µg/ml respectively. The absorbance of each concentration was measured at 248nm.

λ Max :235 nm

Beer's range: 10 µg/mL.

The concentration was calculating using the following formula with R^2= 0.999.

Preparation of standard calibration curve of Nicardipine in 6.8pH buffer

Preparation of standard solution

Standard stock solution of Nicardipine was prepared in 6.8pH buffer. 10 mg of Nicardipine was accurately weighed into10ml volumetric flask and dissolved in small quantity of 6.8pH buffer. The volume was made up with 6.8pH buffer to get a concentration of 1000µg/ml (SS-I) From this 1ml solution was withdrawn and diluted to 10ml to get a concentration of 100µg/ml (SS-II).

Preparation of working standard solutions

Further,from (SS-II) aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml and 1.2ml were pipette into10ml volumetric flasks. The volume was made up with 6.8pH buffer to get the final concentrations of 2, 4, 6, 8, 10 and 12 µg/ml respectively. The absorbance of each concentration was measured at 248nm.

λ Max : 235 nm

Beer's range: 10 µg/ml.

The concentration was calculating using the following formula with R^2= 0.999.

PRECOMPRESSION PARAMETERS [7-10]

Preparation of Bilayer tablets [11-13]

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/cm^2.

Formulation Design

Table 01: Formulation of Immediate release layer (Nicardipine)

Ingredients (mg)	M1	M2	M3	M4	M 5	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	10 0	100

Table 02 : Formulation of Bilayer tablets of Nicardipine

Ingredients (mg)	M6 F1	M6 F2	M6 F3	M6 F4	M6 F5	M6 F6
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

Compression of Bilayer Tablets

The quantity of granules for the sustained-release layer was compressed lightly using 12 stationary double rotary compression machine using 10 inch circular shaped plain punches. Over this compressed layer required quantity of the immediate release granules were placed and compressed to obtain hardness in the range of 6-8 kg/cm2 to form a bilayer tablet of sustained release of Nicardipine and immediate-release of Nicardipine. Then the compressed bilayer tablets were evaluated.

Evaluation of Tablets [14]

Nicardipine tablets were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose and moisture content as per the procedures explained above and the results were tabulated in Table

Post compression parameters

The formulated tablets were evaluated for the following physicochemical parameters.

Thickness

Thickness mainly depends on die filling, physical properties of material to be compressed and compression force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter were measured by using Vernier calipers. Tablet thickness should be controlled within ± 5% variation of standard value.

Hardness

Tablet requires certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packing and shipping. Ten tablets were randomly picked from each formulation during manufacturing and evaluated for hardness using Monsanto hardness tester. It is expressed in kg/cm2.Oral tablets normally have a hardness of 4 to 10kg/cm^2.

Friability

The friability test is closely related to tablet hardness it is usually measured by the use of the Roche friabilator. Ten tablets were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are then dedusted and reweighed and compared with the initial weight. Loss of less than 1% in weight is considered to be acceptable.

$$F\ (\%) \quad \frac{\text{Intial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

Weight Variation Test

Twenty tablets were selected randomly and weighed individually. Average weight was calculated and compared to individual tablet weight. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 03: Weight variation tolerances for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Drug content uniformity

The test is used to ensure that every tablet contains the amount of drug intended with little variation among tablets within a batch. Ten tablets were weighed and crushed in the mortar. The powder equivalent to 25mg drug was dissolved in 6.8 pH phosphate buffer and volume was made up to 100ml to give a concentration of 250µ g/ml. 1ml of this solution was taken and diluted to 10ml to give a concentration of 50µ g/ml.

The absorbance of the prepared solution was measured using UV Visible spectrophotometer (PG Instruments,T60) and the drug concentration was determined from the standard calibration curve by using the regression equation.

$$\text{Concentration } (\mu g/ml) = \frac{\text{absorbance - intercept}}{\text{slope}}$$

$$\text{Drug content (mg)} = \text{concentration X dilution factor}$$

$$\%\ \text{Drug content} = \frac{\text{Drug content}}{\text{Labeled claim}} \text{ X } 100$$

The preparation passes the test if individual drug content is 95-105% of the average content.

***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± 0.5°C 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.

Optimized formulation was subjected to following studies

Release Kinetic [15]

- Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets.
- The model that best fits the release data is selected based on the correlation coefficient (r) value in various models.
- The model that gives high 'r' value is considered as the best fit of the release data.

Mathematical Models are

1. Zero order release model
2. First order release model
3. Higuchi release model
4. Korsmeyer–Peppas release model

Results and discussion

Preformulation Studies

Solubility Studies

Table 04. Solubility studies of Nicardipine

Solvents	Solubility(µg/ml)
Water	0.463
0.1N HCL	0.141
6.8pH Buffer	0.628
7.4pH Buffer	0.473

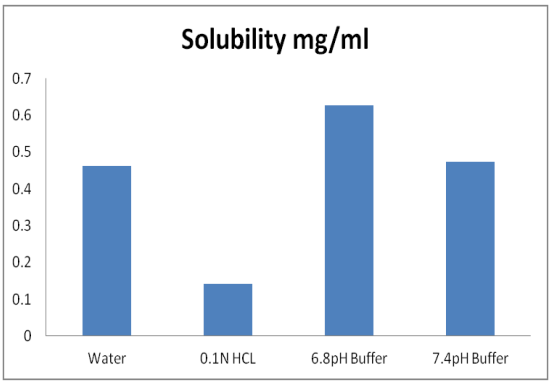

Fig 02: Solubility studies of Nicardipine

From the solubility studies it was observed that the Nicardipine have higher solubility in 6.8pH buffer than the other buffers.

UV spectrum of Nicardipine

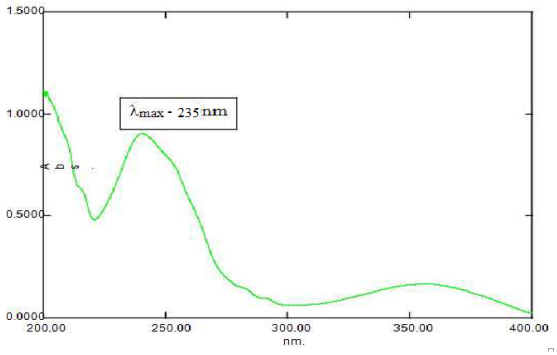

Fig: 03: UV spectra of Nicardipine at 235nm

Table 05: StandardcalibrationcurveofNicardipine in 0.1N HCl

Concentration (µg/mL)	Absorbance
0	0
2	0.134
4	0.270
6	0.384
8	0.510
10	0.635
12	0.761

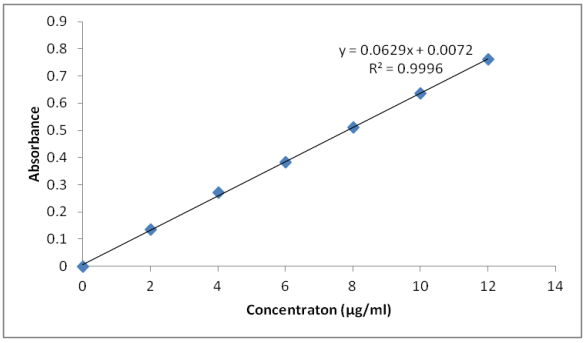

Fig 04: Standard calibration curve of Nicardipine in0.1N HCl at 235nm

Table 06: Standardcalibrationcurveof Nicardipinein 6.8pH buffer at 235nm

Concentration (µg/mL)	Absorbance
0	0
2	0.184
4	0.335
6	0.501
8	0.660
10	0.808
12	0.973

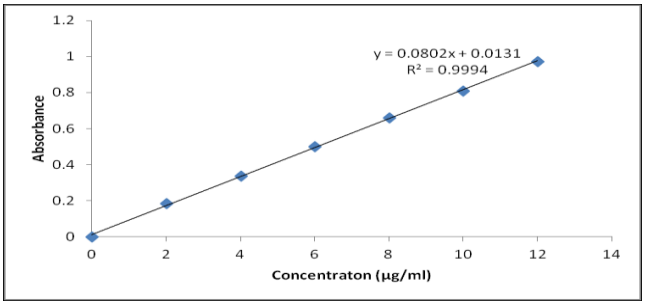

Fig 05:Standard calibration curve of Nicardipine in 6.8pH buffer at 235nm

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.

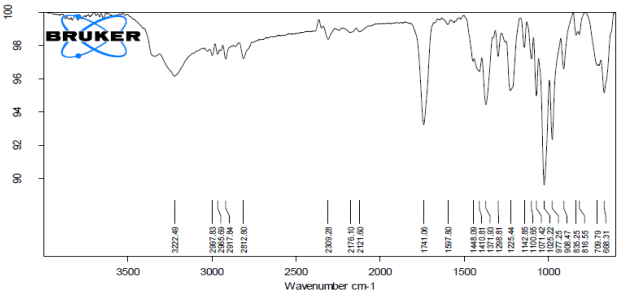

Fig 06: IR spectra of Nicardipine pure

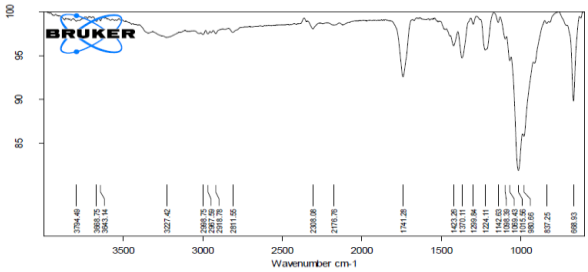

Fig 07: IR spectra of Nicardipine + Excipeints

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)

Table 07: 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 to0.391±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

Table 08:Post Compression parameters

Formulation code	Mean Hardness Kg/cm²	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

Characterization of blend of Floating SR tablets

Table 09: 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

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 10: 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

In vitro dissolution studies

Table 11: Percent Drug Releaseof 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		

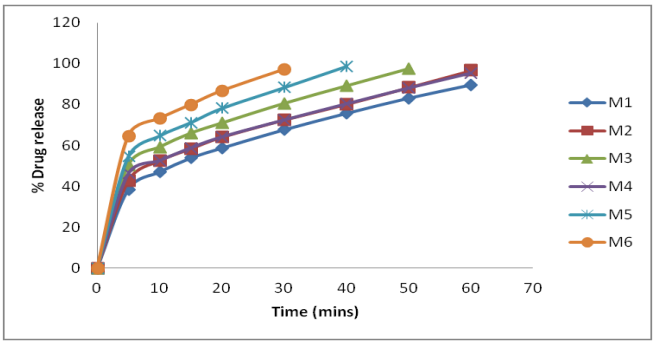

Figure 08: Percent Drug Release versus Time Plots of Nicardipine Tablets M1-M6

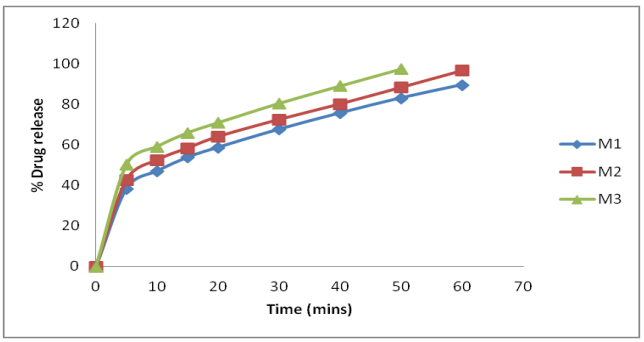

Figure 09: Percent Drug Releaseversus Time Plots of Nicardipine Tablets for M1-M3

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.

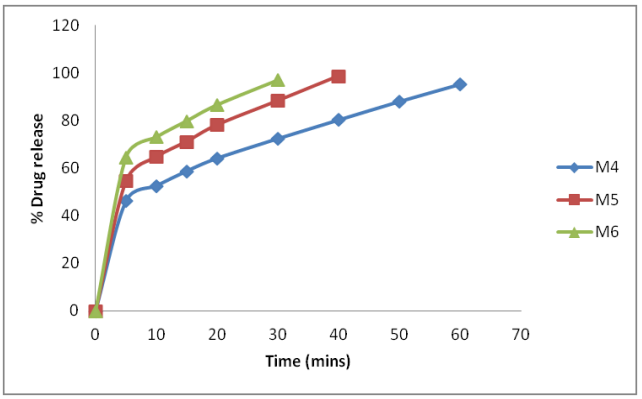

Figure 10: Percent Drug Releaseversus Time Plots of Nicardipine Tablets for M4-M6

The in vitro drug release profiles of immediate release tablets of Nicardipine formulated by using CCS as a super disintegrant in three different ratios in different formulations like M4 with 3mg shows maximum drug release at the end of 60mins i.e., 95.35%. While formulation M5 containing CCS 6mg as superdisintegrant shows 98.75% of drug release at the end of 40mins. While formulation M6 containing CCS 9mg as superdisintegrant shows 97.02% of drug release at the end of 30mins. Above dissolution studies indicate that all the formulations M4 formulation containing CCS (9mg) as the disintegrant had showed faster drug release in 30mins. So M4 formualtion is considered as optimized formulation.

Table 12: Dissolution profile for Bilayer tablets of all formulations (M6F1-M6F6)

Time (MINS)	M6I1	M6I2	M6I3	M6I4	M6I5	M6I6
I.R. Layer						
0	0	0	0	0	0	0
30	97.02	97.02	97.02	97.02	97.02	97.02
S.R. Layer						
30	25.36	20.65	15.63	44.16	38.85	33.56
60	32.19	27.49	22.49	54.61	45.29	41.53
120	40.69	35.46	30.86	63.58	52.19	49.86
180	49.16	44.52	38.98	71.53	59.85	56.49
240	56.36	51.18	46.78	77.95	68.19	62.85
300	64.19	58.49	54.86	85.19	75.49	69.19
360	71.29	64.78	61.29	91.53	83.25	75.49
420	78.46	72.34	67.53	99.26	91.46	81.53
480	86.92	78.53	74.18		98.63	87.49
540	96.53	85.49	80.36			92.36
600		91.56	86.49			97.75
660		97.18	93.05			
720			98.36			

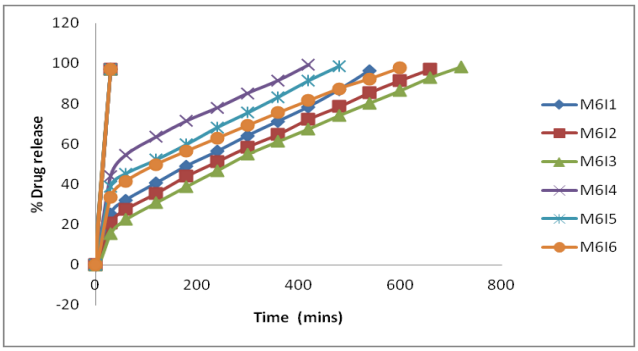

Fig 11: *In-vitro* drug release profile of Bilayer tablets of Formulation M6F1-M6F6

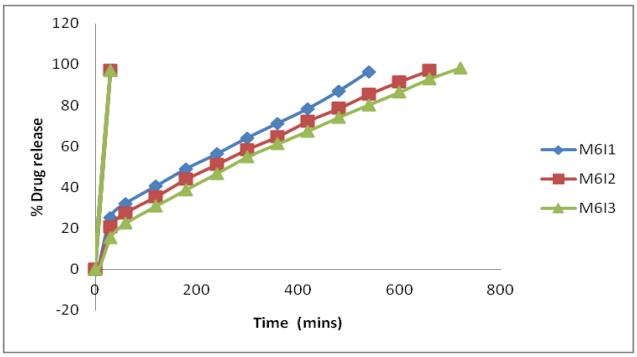

Figure 12: *In-vitro* drug release profile of Bilayer tablets of Formulation M6F1-M6F3

From the in vitro dissolution studies of formulaions M6F1-M6F3 formulated by using Ethyl cellulose in three different ratios. The M6F1 formulation containing Ethyl cellulose (15mg) shows 96.53% of drug release at the end of 540mins.While in M6F2 formulation containingEthyl cellulose (30mg) shows 97.18 % of drug release at the end of 660mins. While in M6F3 formulation containingEthyl cellulose (45mg) shows 98.36% of drug release at the end of 720mins.

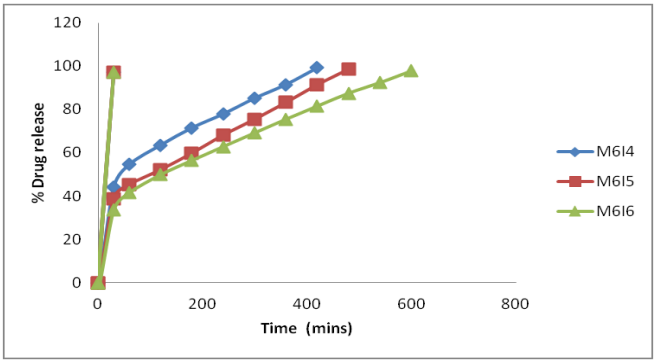

Figure13: *In-vitro* drug release profile of Floating bilayer tablets of Formulation M6I4-M6I6

From the in vitro dissolution studies of formulaions M6F4-M6F6 formulated by using Sodium CMC in different ratios.
The M6F4 formulation containing Sodium CMC (15mg) shows 99.26% of drug release at the end of 420mins.

whereas the M6F5 formulation containing Sodium CMC (30mg) shows 98.63% of drug release at the end of 480mins. whereas the M6F6 formulation containing Sodium CMC (45mg) shows 97.75% of drug release at the end of 600mins. By comparing the in vitro dissolution studies of two polymers like Ethyl cellulose and Sodium CMC, it was observed that the controlled drug delivery was obtained with the ethyl cellulose concentration of 18% in M6F3 formulation than the remaining formualtion. So the drug release kinetics were performed for the formulation M6F3 formulation, as it maintains constant drug release in a sustained manner with optimum swelling and gel forming nature.

Drug releasekinetics of nicardipine bilayer tablets (m6f3)

Zero orderrelease kinetics

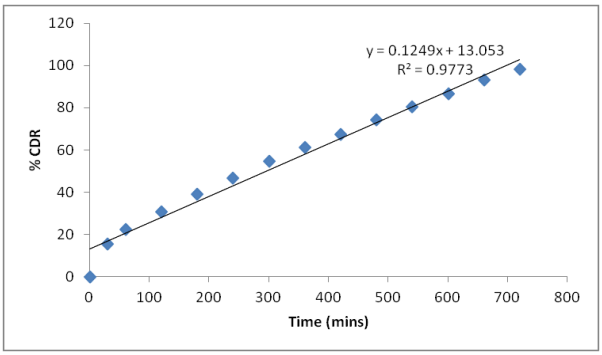

Fig14: Zero order release profile of bilayer tablets of Nicardipine best formulation M6F3

First orderrelease kinetics data of Floating Bilayer tabletsof Nicardipine best formulation M6F3

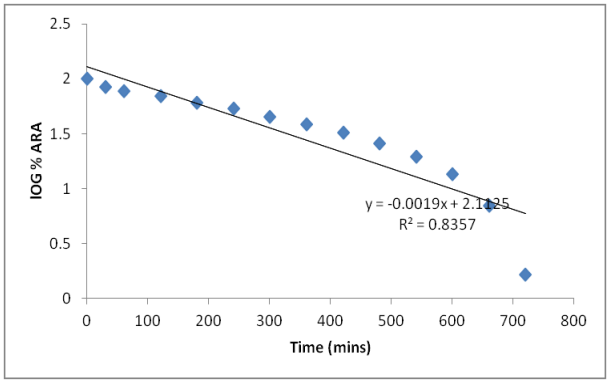

Fig 1 5 : First order release profile of bilayer tablets Of Nicardipine best formulation M6F3

Higuchi Release Kinetics Data of Bilayer Tablets of Nicardipine Best Formulation MF36

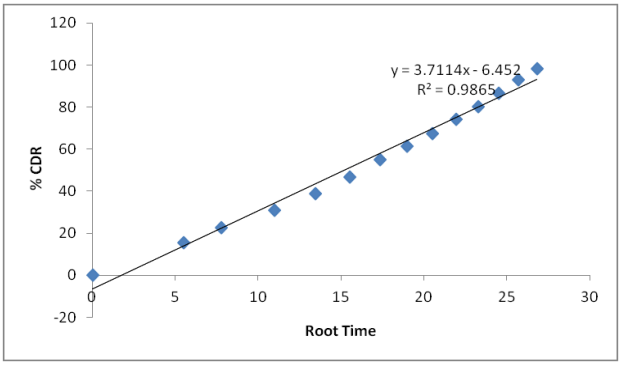

Fig 16: Higuchi release kinetics profile of bilayer tablets of Nicardipine best formulation M6F3

Peppas Release Kinetics Data of Bilayer Tablets of Nicardipine Best Formulation M6F3

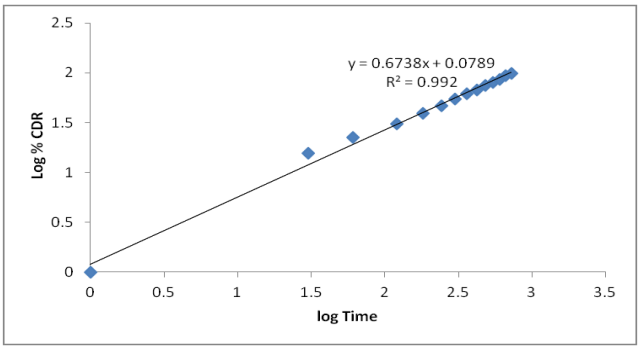

Fig 17: Peppas release kinetics profile of bilayer tablets of Nicardipine best formulation M6F3

Evaluation of drug release kinetics

Release kinetic study

The kinetic release data was computed from the release data obtained from the *in-vitro* dissolution study of the best formulation M6F3 and fitted to the mathematical models; Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

Different Drug Release Kinetics Model Bilayer tablets best formulation M6F3

Table 14: Regression coefficients fitto different drug release kinetics models for best formulation M6F3

Formulation code Best	Zero order	First order	Higuchi	Peppas	
	r^2	r2	r^2	r^2	n value
M6F3	0.977	0.835	0.986	0.992	0. 673

The invitro dissolution data for best formulation M6F3 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation shows R^2 value 0.977 hence it follows zero order release with non- fickian diffusion mechanism.

Summary

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. The tablets were compressed using circular flat-headed punch and die on multi station rotary punching machine. The prepared floating Bilayered tablets were evaluated for hardness, Weight variation, thickness, friability, drug content uniformity, and in-vitro dissolution studies. 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.

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.

Author Contribution

All authors Contributed Equally.

Funding

No Funding from Any Organization and Societies.

Conflict of interest

No Conflict of Intrest

References

1. Chien YW. Oral drug delivery and delivery system in novel drug delivery Systems. 50th ed. New York: Marcel Dekker publication; 1992.
2. Koner P, Saudagar RB, Dharwal J. Gastroretentive drugs: A novel approach towards floating therapy. [Internet]. [Cited on 12th December, 2012]. Available from: http://www.pharmainfo.net/reviews/floating-drug-delivery- systeminnovative-approach-prolong-gastric-retention.
3. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int. J. Pharm tech research. 2009;1(3):623-33
4. Patel M, Sockan GN, Kavitha, Tamizh M. Challenges In The Formulation of Bilayered Tablets: A Review. International Journal of Pharma Research and Development. 2010; 2(10): 3 0- 42.
5. https://en.wikipedia.org/wiki/Nicardipine
6. Pawar RG, Gadhave MV, Jadhac SL, Gaikvad DD. Formulation and evaluation of Miglitol sustained release matrix tablet, International Journal of Pharmaceutical Research and Development, 2011; 4(2): 153-159.
7. Monika Chauhan, Anshul Jain and Satyaveer Singh , Kuldeep Chaurasiya. Formulation and Evaluation of Sustained Release Tablet of Miglitol. World Journal of Pharmacy & Pharmaceutical Sciences 2015, Volume 4, Issue 11, 1194-1205.
8. Nagaraju. R, Rajesh kaza. Formulation and evaluation of bi-layer sustain release tablets of salbutamol and theophylline. Int J Pharm Sci and Nanotech. 2009; 2(3):638-46.
9. Ashraful Islam SM, Hosna Banu and Mostafa Reaj Sahariar. Bilayer tablets of paracetamol and aceclofenac: formulation and evaluation. Int J Pharm Tech. 2011; 3 (4): 3668-81.
10. Chitra Kartikini. S, Jayaprakash. S, Abirami. A, Mohamad Halite S. Design and formulation of Aceclofenac Sodium bi-layer sustain release tablets. Int J Chem Tech Res. 2009; 1(4):1381-5.
11. Costa P., Sousa L. J. M., Modelling and comparison of dissolution profiles, European Journal Pharmaceutical Sciences 2001; 13:2: 123–133.
12. Dash S, Murthy PN, Nath L and Chowdhury P: Kinetic modeling on drug release from controlled drug delivery systems. ActaPoloniaePharmaceutica - Drug Research 2010; 67: 217-223.
13. Marabathuni VJ, Dinesh P, Ravikumar R, Yamini P, Kiran PS, Hussain SP, Rao CM. Chitosan based sustained release mucoadhesive buccal patches containing amlodipine besylate (AMB). Asian J Res Pharm Sci. 2017 Jun 28;7:97-104.
14. Marabathuni VJ, Bhavani M, Lavanya M, Padmaja K, Madhavi N, Babu P, Rao CM. Formulation and evaluation of mouth dissolving Tablets of carbamazepine. Magnesium. 2017 Sep 27;15(30):15.