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FORMULATION DEVELOPMENT AND EVALUATION OF WAX INCORPORATED FLOATING BEADS OF CILNIDIPINE

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Abstract: conventional oral dosage forms having low bioavailability problems due to their rapid gastric transition from stomach, in case of drugs which are less soluble at alkaline pH of intestine. Further drugs which produce their local action in the stomach get rapidly emptied and do not get enough residence time in stomach. Hence, the frequency of dose administration in such cases is increased. To avoid these problems, various efforts have been made to prolong the retention time of drug the stomach. Floating drug delivery system (FDDS) is one of the most important approaches in prolonging the retention time of the drug in the stomach, FDDS is low density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric contents, the drug is released slowly at the desired rate which results in better control of the fluctuations in plasma drug concentration. Based on the mechanism of buoyancy,

Sodium alginate, carnauba wax and bees wax were selected for the preparation of floating alginate wax beads. The identity of Cilnidipine was confirmed by physical characteristics, spectrophotometric analysis such as Ultra violet visible spectrophotometric, Fourier Transform – Infra red and differential thermal calorimetric studies by preparing the floating alginate wax beads of Cilnidipine, the effect of different variables on floating alginate wax beads was studied. The prepared floating beads were evaluated for micromeritic properties, % drug contents, floating lag time, floating time, swelling index and % drug release in 0.1N Hydrochloric acid and its accelerated stability study.

Keywords - Floating Beads, Cilnidipine, Ultraviolet Visible spectroscopy, FTIR.

I. INTRODUCTION

Floating drug delivery system are designed to prolong the gastric residence time after the administration of dosage form and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Conventional pharmaceutical dosage forms with narrow absorption window in the gastro intestine tract have poor absorption. Therefore Floating drug delivery system have been developed, which offer the advantages in prolonging the gastric emptying time. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces the drug waste and improves the drug stability that is less soluble in high environment. This system composed of ion exchange resin beads loaded with bicarbonate and a negatively charged drug tagged to resin. Porous alginate beads are prepared by incorporating CO2 gas generating agents like NaHCO3 and CaCO3. Bicarbonates are merged with stirring into aqueous solution of sodium alginate and then mixture is added to solution of calcium chloride with 10% acetic acid. So due to acetic acid and bicarbonate, CO2 gas is generated and simultaneously gelling of beads are occurred by calcium ions and CO2 which goes out from beads during stirring and creating porous structures in calcium alginate floating beads.

MECHANISM OF FLOATING SYSTEM

Various attempts are made to obtain retention of dosage form in the stomach by increasing RT of stomach. These include introduction of different gastro retention dosage forms as floating systems (gas generating system and swelling and expanding system), muco-adhesive system, high density system, modified shape systems, gastric– emptying delaying devices and co administration of gastric empting delaying drugs. From this the floating drug delivery systems (FDDS) is most commonly used. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. When the system floats on gastric contents the drug is released slowly at the desire rate from the system. After the drug is released, the residue is emptied from the stomach. This results in increasing the gastric empting time of stomach as well as controlling the fluctuations in PDC.

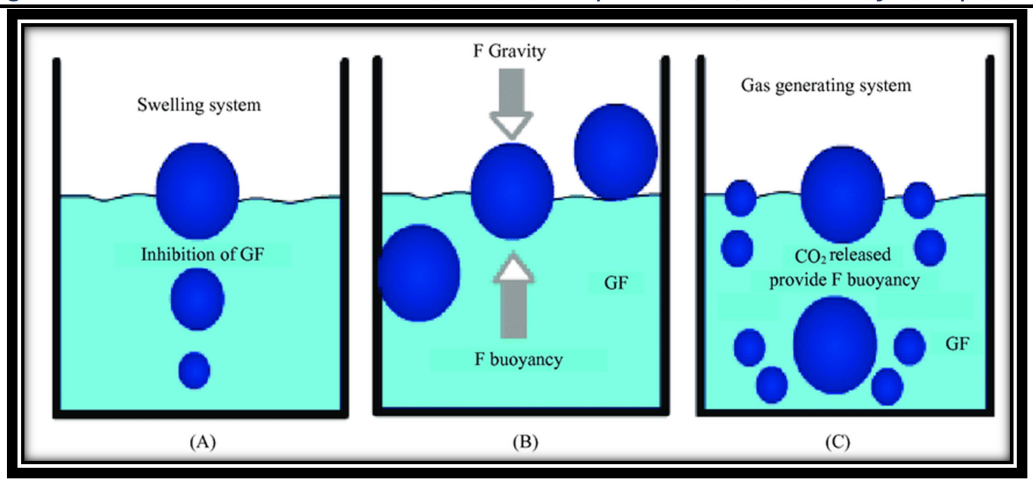

FIG. NO.1: MECHANISM OF FLOATING DRUG DELIVERY

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

a) Used for local action in the stomach.
b) In the treatment of peptic ulcer disease.
c) Used for the delivery of drugs with narrow absorption window in small intestine.
d) Reduced dosing frequency.
e) Improved bioavailability of drugs.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS

a. Drugs that cause irritation to the gastric mucosa cannot be formulated in gastro- retentive systems.
b. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach unwanted.
c. Furthermore, other drugs, such as isosorbide di-nitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention systems.

II. EXPERIMENAL WORK

PREFORMULATION STUDY OF DRUG

Organoleptic properties

The sample of Cilnidipine was checked for organoleptic properties such as colour and odour.

Melting point determination

Melting point of Cilnidipine was determined by taking small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate.ca

Solubility

Solubility of Cilnidipine was carried out using different solvent such as water, methanol, Phosphate buffer (pH 6.8), 0.1N Hydrochloric acid, 0.1N Sodium hydroxide etc.

Ultra Violet Visible Spectroscopy Study
Preparation of stock solution in 0.1N HCl

100 µg/ml stock solution of Cilnidipine was prepared by dissolving 10 mg of drug in suitable volume of 0.1N Hydrochloric acid with continuous shaking.

Determination of λmax of Cilnidipine in 0.1N HCl

Solution of Cilnidipine (100µg/ml) and its maximum absorption identified through UV spectrophotometer by scanning within the wavelength region of 200 – 400 nm against 0.1N Hydrochloric acid as a blank. Obtained spectra showing the peak with highest absorbance (λmax = 240 nm) was considered as absorbance maximum of the drug.

Preparation of calibration curve of Cilnidipine in 0.1N HCl

The prepared stock solution was subsequently diluted to get 2-10 µg/ml. The resulting solutions absorbance was measured at obtained λmax using UV spectrophotometer against blank of 0.1N Hydrochloric acid. This procedure was carried out in triplicate. The results obtained were tabulated and plotted a calibration curve of absorbance versus concentration.

Preparation of stock solution in phosphate buffer pH 6.8

The 100 µg/ml stock solution of Cilnidipine was prepared by dissolving 10 mg of drug in suitable volume of phosphate buffer pH 6.8 with continuous shaking.

Determination of λmax of Cilnidipine in phosphate buffer pH 6.8

Solution of Cilnidipine (100µg/ml) and its maximum absorption identified through UV spectrophotometer by scanning within the wavelength region of 200 – 400 nm against phosphate buffer pH 6.8 as a blank. Obtained spectra showing the peak with highest absorbance (λmax= 240 nm) was considered as absorbance maximum of the drug.
Preparation of calibration curve of Cilnidipine in phosphate buffer pH 6.8: The prepared stock solution was subsequently diluted to get 2-10 µg/ml. The resulting solutions absorbance was measured at obtained λmax using UV spectrophotometer against blank of phosphate buffer pH 6.8. This procedure was carried out in triplicate. The results obtained were tabulated and plotted a calibration curve of absorbance versus concentration.

Preparation of stock solution in methanol

The 100 µg/ml stock solution of Cilnidipine was prepared by dissolving 10 mg of drug in suitable volume of methanol with continuous shaking.

Determination of λmax of Cilnidipine in methanol

Dilute solution of Cilnidipine (10µg/ml) prepared from the above stock solution using solution and its maximum absorption identified through UV spectrophotometer by scanning within the wavelength region of 200 – 400 nm against methanol as a blank. Obtained spectra showing the peak with highest absorbance (λmax=240 nm) was considered as absorbance maximum of the drug.
Preparation of calibration curve of Cilnidipine in methanol
The prepared stock solution was subsequently diluted to get 2-10 µg/ml. The resulting solutions absorbance was measured at obtained λmax using UV spectrophotometer against blank of methanol. This procedure was carried out in triplicate. The results obtained were tabulated and plotted a calibration curve of absorbance versus concentration.

Characterization of Excipients

The description of all the additives was similar to those reported in the literature. The excipients were evaluated for their appearance, colour. Sodium Alginate, Carnauba wax and Calcium chloride are the additives were used in the formulations.

Fourier Transform Infra-Red Spectroscopy (FTIR)

The FTIR spectrum of Cilnidipine was recorded at wave number 4000 to 400 cm- 1 using Fourier transform spectrophotometer (Mode - FTIR, Bruker).
Method used for analysis was ATR. However, ATR method is able to measure powder sample directly. Attenuated total reflection (ATR) method involves pressing the sample against a high-refractive index prism and measuring the infrared spectrum using infrared light that is totally internally reflected in the prism. A zinc selenide (ZnSc) or germanium (Ge) prism was used in the ATR accessory.

Compatibility Study
Fourier Transform Infra-Red Spectroscopy (FTIR)

The compatibility study was carried out by using Fourier transform infrared spectrophotometer (BRUKER). FTIR study was carried on pure drug and physical mixture of drug and polymer. Physical mixtures were prepared and samples were kept for 1 month at room temperature. Infrared absorption spectrum of Cilnidipine was recorded over the wave number 4000 to 400 cm-1 using Fourier Transform spectrophotometer (Bruker, ECO- ATR).

Differential Scanning Colorimetry (DSC) of Drug

The DSC measurements were performed on a DSC, Shimadzu, Japan differential scanning calorimeter with thermal analyser. All accurately weighed sample were placed in a sealed aluminium pans, before heating under nitrogen flow (10 ml/min) at a scanning rate of 100C per min from 25 to 3000C. An empty aluminium pan was used as reference.

Differential Scanning Colorimetry (DSC) of Formulation
The DSC measurements were performed on a DSC 60, Shimadzu, Japan differential scanning calorimeter with thermal analyzer. All accurately weighed samples were placed in a sealed aluminium pans, before heating under nitrogen flow (10 ml/min) at a scanning rate of 100C per min from 25 to 3000C. An empty aluminium pan was used as reference.

Formulation and Development
Preparation of floating beads

Composition of formulation:

TABLE NO. 1: COMPOSITION OF FORMULATION

Sr. NO.	Ingredient (gm)	F1	F2	F3	F4	F5	F6
1	Cilnidipine	0.2	0.2	0.2	0.2	0.2	0.2
2	Sodium Alginate	2	2	2	2	2	2
3	White Bees Wax	1	2	3	-	-	-
4	Carnauba Wax	-	-	-	1	2	3

The following steps were carried for its preparation:

Step 1. Sodium Alginate, Wax and drug was mixed thoroughly.

Step 2. The pre-weighed amount of wax was melted in the porcelain dish on the heating water bath.

Step 3. The mixture formed was heated to the temperature above the melting point of the wax.

Step 4. The molten wax was dispersed in the preheated mixture using hot plate with magnetic stirrer.

Step 5. After stirring for 15 min the above solution was filled into the 22G syringe and air bubbles were removed.

Step 6. The solution was added drop wise into the 2 % calcium chloride solution.

Step 7. After addition of solution the beads are formed. The beaker was kept aside for 15 min.

Step 8. The beads were filtered from calcium chloride solution. The beads were rinsed thoroughly with distilled water and dried at room temperature.

Evaluation of Floating Beads

Physical appearance

All the prepared floating beads formulations of Cilnidipine was checked for their size, shape and colour.

Micromeritic properties

All the prepared floating beads formulation of Cilnidipine was checked for the Bulk density, Tapped density, Carr's index, Hausner's ratio.

Bulk density: The bulk density was obtained by dividing the mass of powder by the bulk volume. The sample equivalent to 7.5 mg was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and unsettled volume (V0) was noted. The bulk density was calculated by the formula:

$$\text{Bulk Density:} \quad \frac{M}{Vo}$$

Where, M = mass of powder taken and

V0 = Apparent unsettled volume.

Tapped density: The tapped density was determined by mechanically tapping the measuring cylinder or by using the digital bulk density tester (Meta Lab) USP Model no.I and the tapped volume were noted (USP, 2006). The tapped density was calculated by the formula:

$$\text{Tapped Density} = \frac{M}{Vt}$$

Where, M = weight of powder,

Vt = tapped volume of powder in cm3

Hausner's ratio: Hausner's ratio gives an idea regarding the flow of the blend to the apparent density. Hausner's ratio was calculated as;

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

TABLE NO.2: RELATIONSHIP BETWEEN HAUSNER'S RATIO AND FLOW PROPERTY

Hausner's Ratio	Flow property
1-1.11	Excellent
1.12-1.18	Good
1.26-1.34	Poor

Carr's index: The carr's index measures of the propensity of the powder to be compressed. The packing ability of the drug was evaluated from change in the volume, which is due to rearrangement of packing occurring during tapping (USP, 2006). It is indicated as Carr's compressibility index (CI) and can be calculated as follows

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

TABLE NO.3: RELATIONSHIP BETWEEN % COMPRESSIBILITY AND FLOW PROPERTY

% Compressibility	Flow property
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
< 40	Extremely poor

Percentage Yield

All the prepared formulations of Cilnidipine were checked for their percentage yield.

$$\text{Percentage yield} = \frac{\text{Total mass of formulation}}{\text{Total mass of raw materials}} \times 100$$

Determination of drug content and drug entrapment efficiency

The 150 mg of floating beads were dissolved in 0.1 N Hydrochloric acid undersonication and filtered. The drug content was assayed using UV- spectrophotometer (V – 630, Shimadzu Co Ltd., Japan) at 240 nm after suitable dilution with 0.1 N Hydrochloric acid. Percent drug content and entrapment efficiency was determined using formula [65]

$$\% \text{ Drug content} = \frac{\text{Actual drug content}}{\text{Total drug amount taken}} \times 100$$

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Floating lag time and floating time

The formulated bead sample (n=20) were placed in a beaker filled with 0.1N HCl (pH1.2) solution. Temperature was maintained at 37 0C. The floating time of beads were observed for 12 hrs. The preparation was considered to have buoyancy in the test solution only when all the beads floated in it. The time the formulation took emerge on the surface of the medium (floating lag time) and the time for which the formulation remains floating on the surface of the medium (floating time) were noted [66]

Swelling studies

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus I. The basket containing beads put in a beaker containing 100 ml of 0.1N HCl (pH 1.2) maintained at 37 0C. The beads were periodically removed at predetermined intervals and weighed. Then swelling ratio was calculated as per the following formula.

$$\text{Swelling index} = \frac{Ws - Wo}{Wo} \times 100$$

Where, Ws = weight of swollen beads,
Wo = weight of dried beads

Particle size determination

The particle size of beads was determined by the dry state using optical microscopy method. The stage micrometer and eyepiece micrometer were used for the measurement of the particle size. The size of the beads present in the 1cm3 area of the slide was counted.

Surface characterization

Surface characterization of beads were examined with a scanning Electron Microscopy (Diya labs, Airoli, Mumbai) beads were mounted on metal grids using double-sided tape.

In- vitro drug release study

The release of Cilnidipine from sustained release floating wax bead was determined using USP dissolution apparatus I at 50 rpm. The dissolution medium used 900ml of 0.1N HCl (pH1.2) and temperature was maintained at 370C. A sample (5ml) was withdrawn from the dissolution apparatus at 0 min., 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr. The samples were filtered through Whatman filter paper and analysed using UV method. Cumulative % drug release was calculated and observed. The dissolution of the formulation was compared with the 210 mg of the capsule containing 10 mg of the drug.

Best fit kinetic model for optimized formulation

The data obtained from study of diffusion kinetics of the optimized formulation was studied to obtain the best fit model. The best fitted model is the one which gives the highest R2 value and least slope value.

Stability studies

Stability study of the formulation which gave maximum dissolution rate was carried out to point out any visual physical or chemical change made in the formulation after storing it at elevated temperature and humidity conditions. The optimized formulation was store in ambient colour bottle and stored at 400 C ± 20C and 75% ± 5% Relative humidity for three months. Floating wax beads was analysed for the drug content

III. RESULTS AND DISCUSSION

Organoleptic properties:

TABLE NO. 4: ORGANOLEPTIC PROPERTIES OF CILNIDIPINE

S. No.	Properties	Observation
1	Appearance	Crystalline powder
2	Colour	Off-white
3	Odour	Odourless

Melting point determination:

The melting point of Cilnidipine was given in table 5. The melting point of thedrug matches with values found in literature.

TABLE NO. 5: MELTING POINT OF CILNIDIPINE

Sr. No.	Drug	Melting point	
1.	Cilnidipine	Literature	Observed
		108-111 ^{0}C	110^{0}C

Solubility

Solubility of Cilnidipine was determined in different solvent and given in table.The results were similar to those mentioned in literature.

TABLE NO. 6: SOLUBILITY DETERMINATION OF CILNIDIPINE

Sr. No.	Solvent	Solubility
1	Methanol	Soluble
2	0.1 N Hydrochloric acid	Soluble
3	NaOH	Soluble
4	Water	poorly soluble
5	Phosphate buffer (pH 6.8)	Soluble

Ultraviolet –Visible spectroscopy study

Preparation of stock solution

The 100 µg/ml stock solution of Cilnidipine was prepared by dissolving 10 mgof drug in suitable volume of 0.1 N Hydrochloric acids with continuous shaking.

Determination of λmax of Cilnidipine

The UV spectrum of Cilnidipine solution (10µg/ml) exhibited wavelength of absorbance maximum at 240nm. This is near to the reported value. However, Keeping in mind the probable concentrations likely to be encountered while carrying out the In-vitro release studies and considering the predicted theoretical λmax involved, the working λmax was decided as 240nm. The spectrumof Cilnidipine is shown in fig 2.

TABLE NO.7: MAXIMUM WAVELENGTH OF CILNIDIPINE IN 0.1NHYDROCHLORIC ACID (PH 1.2)

Solvent	Wavelength of maxima (nm)
0.1 N Hydrochloric acid (pH 1.2)	240 nm

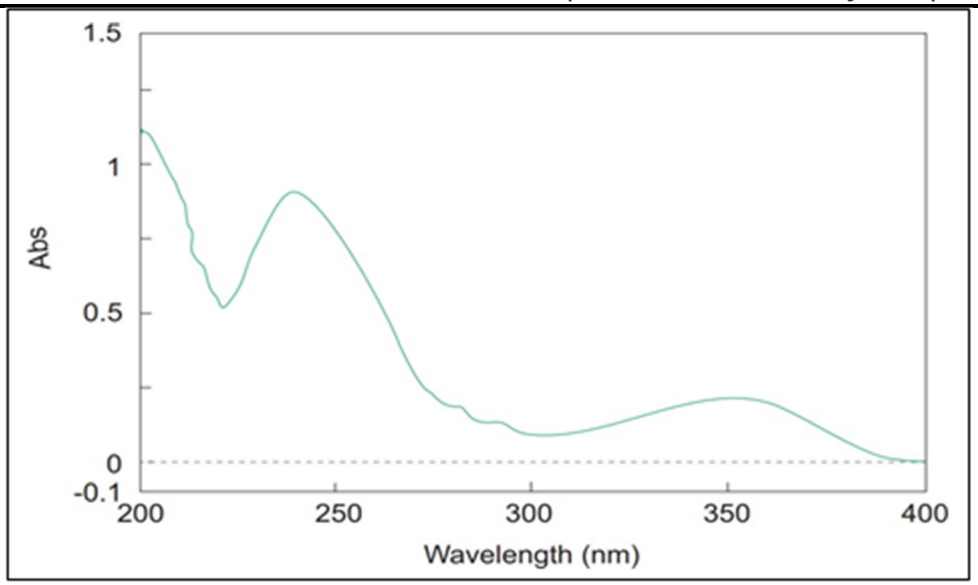

FIG.NO.2: SPECTRUM OF CILNIDIPINE IN 0.1N HCL

Calibration curve of Cilnidipine in 0.1N Hydrochloric acid(pH 1.2)

The calibration curve was found to linear in the concentration range of 2-10 µg/ml having coefficient of regression value R2 = 0.9996 and slope y = 0.0995x- 0.0689 (fig.no.3).

TABLE NO. 8: ABSORBANCE VALUE OF CILNIDIPINE IN 0.1N HYDROCHLORIC ACID (PH 1.2)

Sr, No.	Concentration	Absorbance
1	2	0.1248
2	4	0.3364
3	6	0.5319
4	8	0.7198
5	10	0.9284

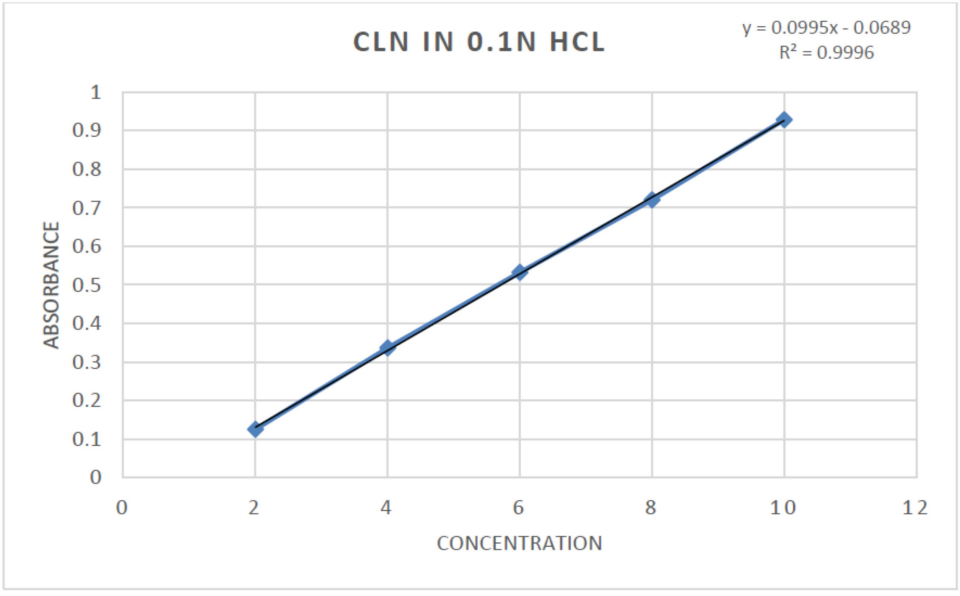

Fig. No.3: Calibration curve of Cilnidipine in 0.1N HCl

Preparation of stock solution in phosphate buffer pH 6.8

The 100 µg/ml stock solution of Cilnidipine was prepared by dissolving 10 mg of drug in suitable volume of phosphate buffer pH 6.8 with continuous shaking.

Determination of λmax of Cilnidipine in phosphate buffer pH 6.8

The UV spectrum of Cilnidipine solution (10µg/ml) exhibited wavelength of absorbance maximum at 240nm. This is near to the reported value. However, Keeping in mind the probable concentrations likely to be encountered while carrying out the In-vitro release studies and considering the predicted theoretical λmax involved, the working λmax was decided as 240nm. The spectrum of Cilnidipine is shown in fig 4.

TABLE NO. 9: MAXIMUM WAVELENGTH OF CILNIDIPINE IN PHOSPHATE BUFFER PH 6.8

Solvent	Wavelength of Maxima (nm)
Phosphate buffer pH 6.8	240 nm

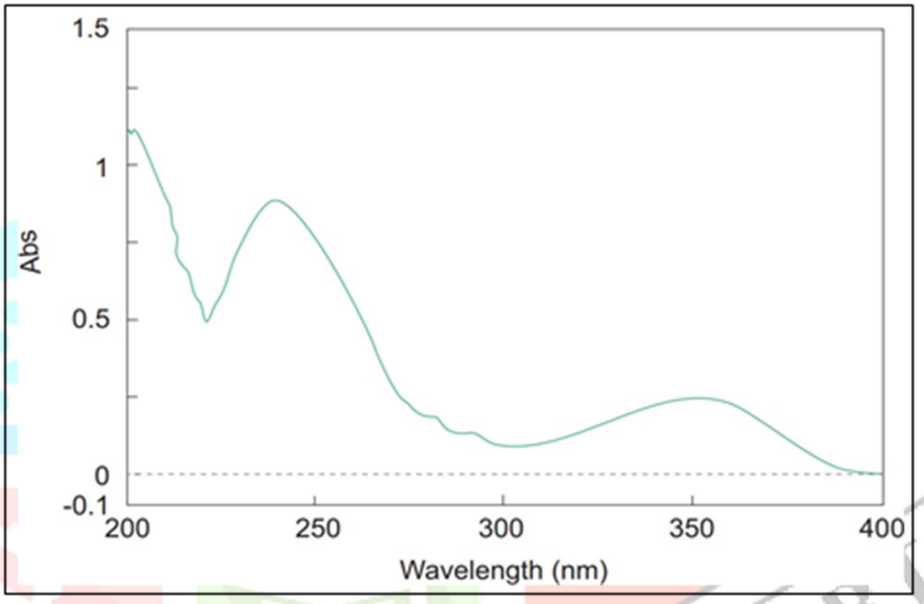

FIG.NO. 4: SPECTRUM OF CILNIDIPINE IN PHOSPHATE BUFFER PH 6.8

Calibration curve of Cilnidipine in phosphate buffer pH 6.8

The calibration curve was found to linear in the concentration range of 2-10 µg/ml having coefficient of regression value R2 = 0.9994 and slope y = 0.1002x - 0.0858 (fig. no. 5)

TABLE NO. 10: ABSORBANCE VALUE OF CILNIDIPINE IN PBS PH 6.8

Sr. No	Concentration	Absorbance
1	2	0.1201
2	4	0.3169
3	6	0.5047
4	8	0.7107
5	10	0.9254

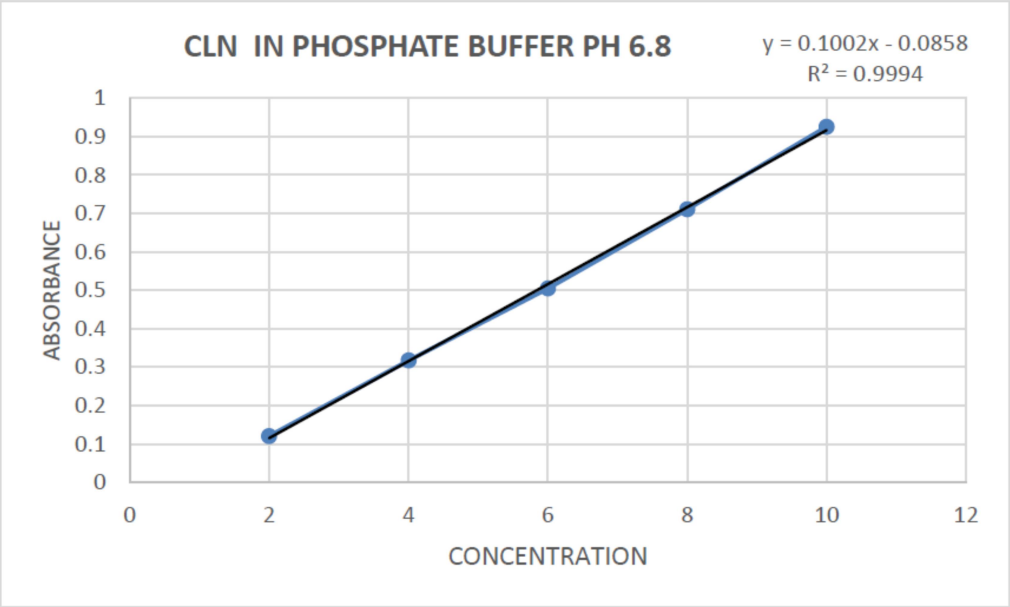

Fig. No. 5: Calibration curve of Cilnidipine in PBS pH 6.8

Preparation of stock solution in methanol

The 100 µg/ml stock solution of Cilnidipine was prepared by dissolving 10 mg of drug in suitable volume of methanol with continuous shaking.

Determination of λmax of Cilnidipine in methanol

The UV spectrum of Cilnidipine solution (10µg/ml) exhibited wavelength of absorbance maximum at 240nm. This is near to the reported value. However, Keeping in mind the probable concentrations likely to be encountered while carrying out the In-vitro release studies and considering the predicted theoretical λmax involved, the working λmax was decided as 240 nm. The spectrum of Cilnidipine is shown in fig 6

TABLE NO. 11: MAXIMUM WAVELENGTH OF CILNIDIPINE IN METHANOL

Solvent	Wavelength of maxima (nm)
Methanol	240

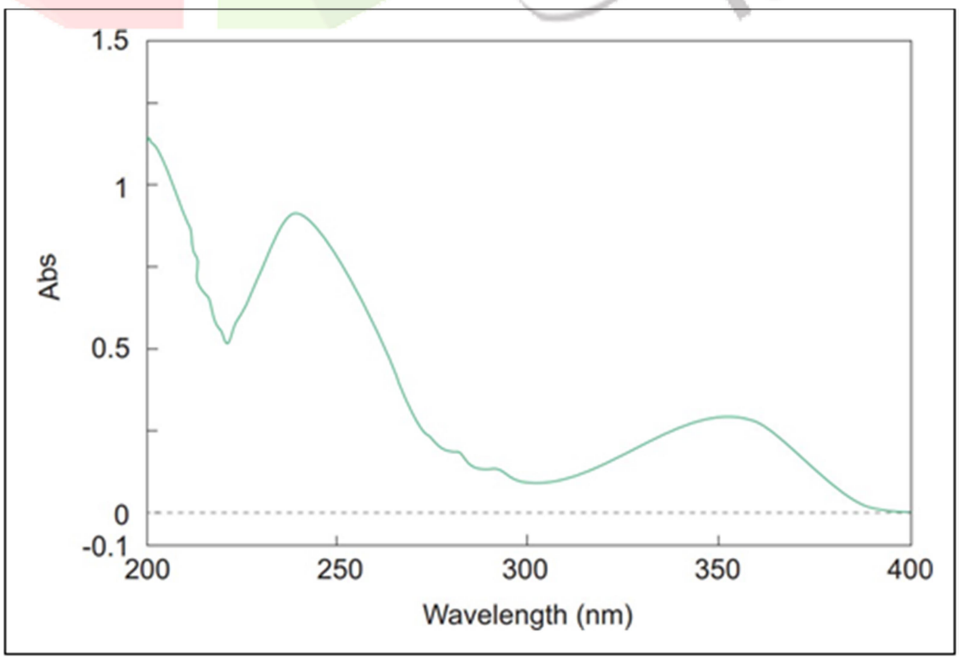

FIG NO. 6: SPECTRUM OF CILNIDIPINE IN METHANOL

Calibration curve of Cilnidipine in methanol

The calibration curve was found to linear in the concentration range of 02 – 10µg/ml having coefficient of regression value R2 = 0.9993 and slope y = 0.0986x - 0.0513

TABLE NO. 12: ABSORBANCE VALUE OF CILNIDIPINE IN METHANOL

Sr, No.	Concentration	Absorbance (nm)
1	2	0.1367
2	4	0.3482
3	6	0.5494
4	8	0.7398
5	10	0.9267

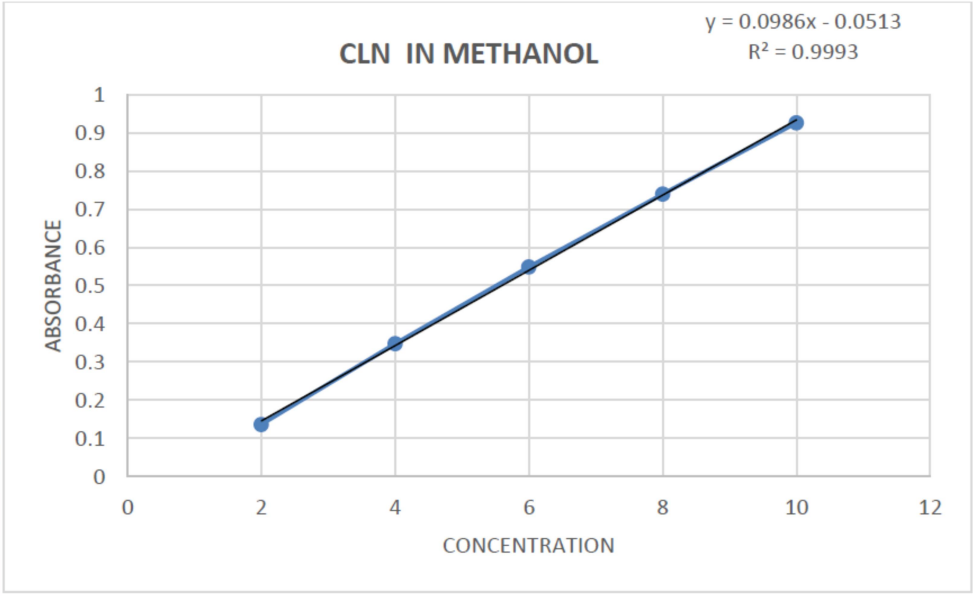

FIG. NO. 7: CALIBRATION CURVE OF CILNIDIPINE IN METHANOL

Fourier Transform Infra- Red Spectroscopy (FTIR)

Infrared spectrum of Cilnidipine is shown in fig.8.The major peaks observed and corresponding functional groups are given in Table 13. Infra-red spectrum shows peak characteristics of structure of Cilnidipine

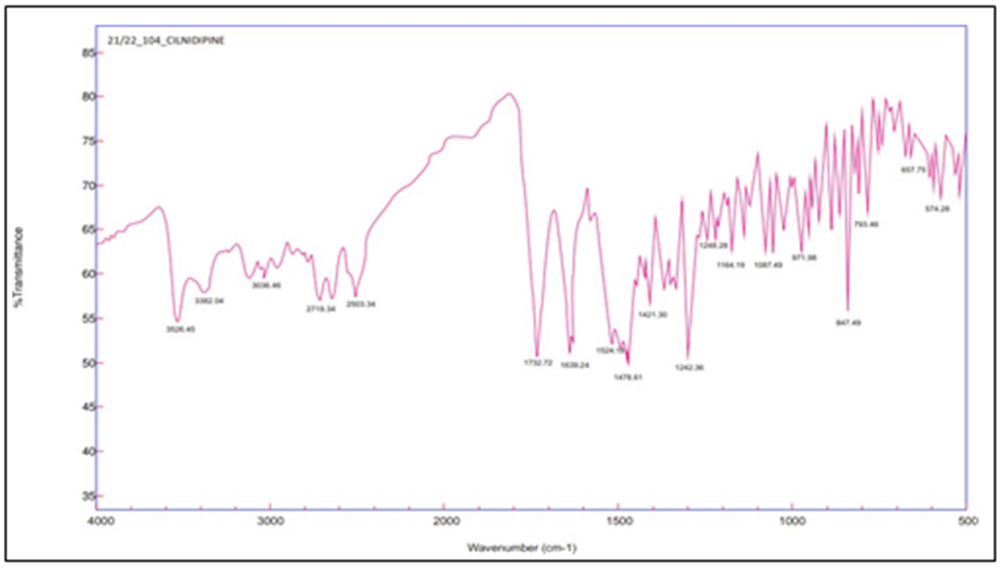

FIG. NO.8: FTIR SPECTRUM OF CILNIDIPINE

TABLE NO.13: INTERPRETATION OF FTIR SPECTRUM OF CILNIDIPINE

Functional Group	Reported Peak(cm^{-1})	Observed Peak (cm^{-1})
O-H Stretch	2900-2945	3526.45
N-H Stretch	2235-2255	3382.04
C=O Stretching	1510-1538	2719.34
C=C Aromatic Stretch	1300-1340	1732.72
C-H bending (Aromatic)	1425-1470	1478.61

Differential scanning colorimetric studies (DSC):

DSC thermogram of Cilnidipine is shown in fig.9 The DSC analysis of Cilnidipine against reported values are given in Table 14. The DSC thermogram peak value matches with value found in literature.

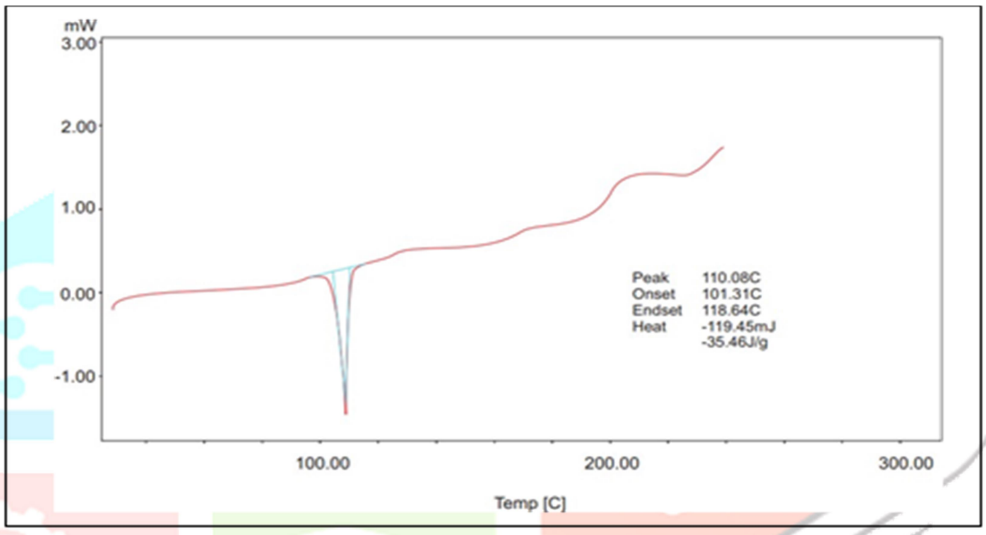

FIG. NO. 9: DSC THERMOGRAM OF CILNIDIPINE

TABLE NO. 14: INTERPRETATION OF DSC THERMOGRAM OF CILNIDIPINE

Observed value	110.08 ^{0}C
Peak	110.08 ^{0}C
Onset	101.31 ^{0}C
End	118.64 ^{0}C
Heat	-119.45mJ

The above fig shows melting point of Cilnidipine giving sharp peak at 110.080C with heat -119.45 mJ

Compatibility study

Fourier Transform Infra-Red Spectroscopy (FTIR)

To check the interaction between drug and polymer, used in the formulations, FTIR studies were performed. In the study it was found that all the prominent peaks were present in individual graph of Cilnidipine and polymers were also present in the FTIR of the physical mixture of drug and polymer. Thus we can say that there was no interactions between drug and polymer were observed. The interpretation of Infra-red spectra of Cilnidipine was shown in Table 15.

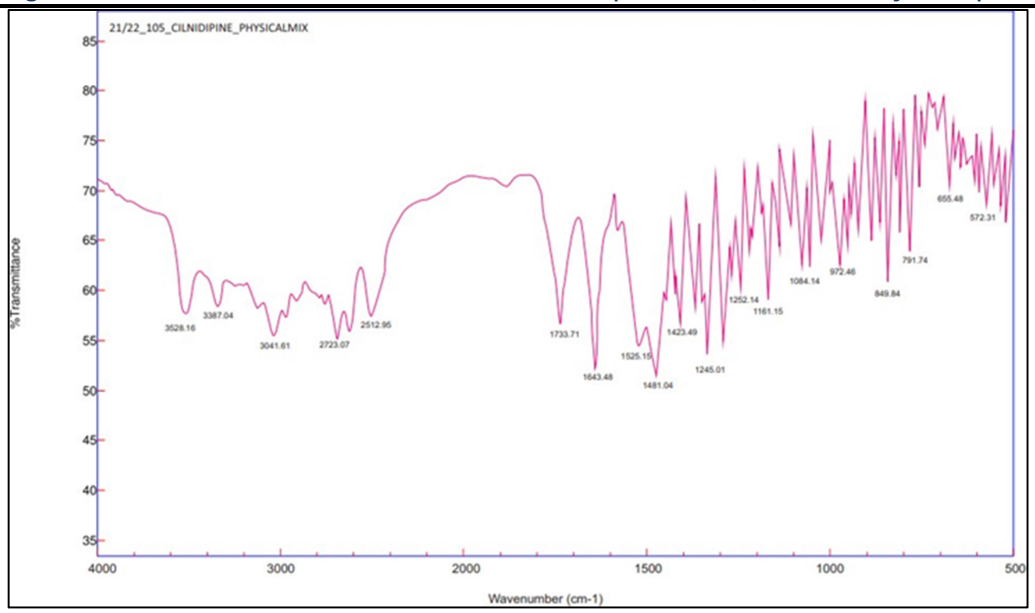

FIG. NO. 10: FTIR SPECTRUM OF DRUG POLYMER COMPATIBILITY STUDY

TABLE NO. 15: INTERPRETATION OF FTIR SPECTRA OF PHYSICAL MIXTURE

Functional Group	Peaks	
	Pure Drug	Physical Mixture
O-H Stretch	Yes	Yes
N-H Stretch	Yes	Yes
C=O Stretching	Yes	Yes
C=C Aromatic Stretch	Yes	Yes
C-H bending (Aromatic)	Yes	Yes

The FTIR spectrum of physical mixture retained all characteristics peaks visible in the drug alone.

Micromeritic properties

The micromeritic properties (Bulk density, Tapped density, Carr's index,Hausner's ratio) of all the formulated batches was measured.

TABLE NO. 16: MICROMERITIC PROPERTIES OF THE FORMULATION

Batch Code	Bulk Density (gm/ml) ± SD	Tapped Density (gm/ml) ± SD	Carr's index ± SD	Hausner's ratio ± SD
F1	0.366 ± 0.012	0.444 ± 0.016	17.8 ± 5.22	1.21 ± 0.08
F2	0.353 ± 0.005	0.442 ± 0.019	19.92 ± 3.20	1.25 ± 0.05
F3	0.357 ± 0.013	0.474 ± 0.014	24.59 ± 4.78	1.33 ± 0.08
F4	0.361 ± 0.005	0.447 ± 0.025	19.10 ± 5.34	1.24 ± 0.08
F5	0.366 ± 0.012	0.428 ± 0.002	14.64 ± 2.42	1.17 ± 0.03
F6	0.365 ± 0.009	0.436 ± 0.008	16.13 ± 2.37	1.19 ± 0.03

Floating lag time and floating time

The gel beads samples (n=20) were placed in the beaker filled with 50ml of 0.1 N HCl (pH 1.2) solution. Temperature was maintained at 370C. The floating time of beads was observed for 20hrs. The preparation was considered to have buoyancy in the test solution only when all the gel beads floated in it. The timethat formulation took to emerge on the medium surface (floating lag time) and time the formulation constantly floated on the dissolution medium surface (floating time) were noted

TABLE NO. 17: FLOATING LAG TIME AND FLOATING TIME OF FORMULATIONS

Sr. No.	Batch	Floating lag time (min.)	Floating time (hrs.)
1	F1	1.63± 0.05	> 12
2	F2	1.08± 0.08	> 12
3	F3	1.23± 0.01	> 12
4	F4	1.27± 0.03	> 12
5	F5	1.20± 0.01	> 12
6	F6	1.18± 0.07	> 12

The above table showed floating lag time in the range of 1.08 – 1.63 min. and floating time >12hr for all formulations F1-F6. This is due the increase in the concentration of the carnauba wax.

Swelling studies

Beads were studied for their swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads were put ina beaker containing 100ml of 0.1N HCl (pH 1.2) maintained at 37^{O}C. The beads were periodically removed at predetermined intervals and weighed.

TABLE NO. 18: SWELLING INDEX OF FORMULATIONS

Sr. No.	Batch Code	Swelling ± SD
1	F1	12.64 ± 0.12
2	F2	13.05 ± 0.08
3	F3	18.56 ± 0.16
4	F4	19.84 ± 0.03
5	F5	14.05 ± 0.04
6	F6	12.31 ± 0.03

For all prepared batches (F1-F6), percent swelling ratio was found to be in the range of 12.31-19.84 %. The F4 batch showed the maximum swelling index. This is because of the lipophillic nature of the carnauba wax which affected theswelling of the beads.

In vitro drug release study

The In vitro drug release study of different formulation

TABLE NO. 19: IN-VITRO DRUG RELEASE OF DIFFERENT BATCHES OF THEFORMULATION

Time (hr)	F1	F2	F3	F4	F5	F6
0	**0**	**0**	**0**	**0**		
1	9.15	10.15	8.13	9.48	5.16	7.51
2	21.6	22.36	23.64	25.16	15.02	18.48
4	38.16	39.18	42.01	42.15	26.15	32.14

6	52.87	53.15	54.1	55.94	40.15	49.48
8	71.54	73.05	65.26	76.51	49.81	60.19
10	87.94	88.51	75.14	92.61	53.01	71.5
12	92.31	94.16	85.14	98.16	61.74	82.14

Maximum drug release 98.16% was shown by F4 batch. The data also suggested that floating beads formulation were capable to produce linear drugrelease for longer period of time. Drug release profile of formulation F1 to F6shown in Fig 11 and dissolution profile F1 to F6 signified sustained drug release.

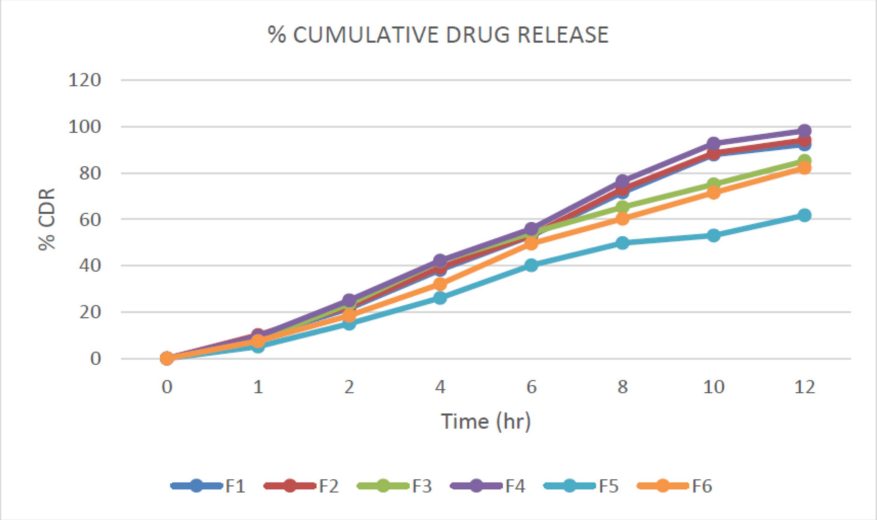

FIG. NO. 11: DRUG RELEASE PROFILE OF FORMULATIONS F1-F6

Kinetic model for F4 batch

In order to investigate the mode of release from floating beads data were analysed with following mathematical model.

A. Zero order kinetic
B. First order kinetic
C. Higuchi equation
D. Korsemeyer-peppas equation

A. Zero order kinetic

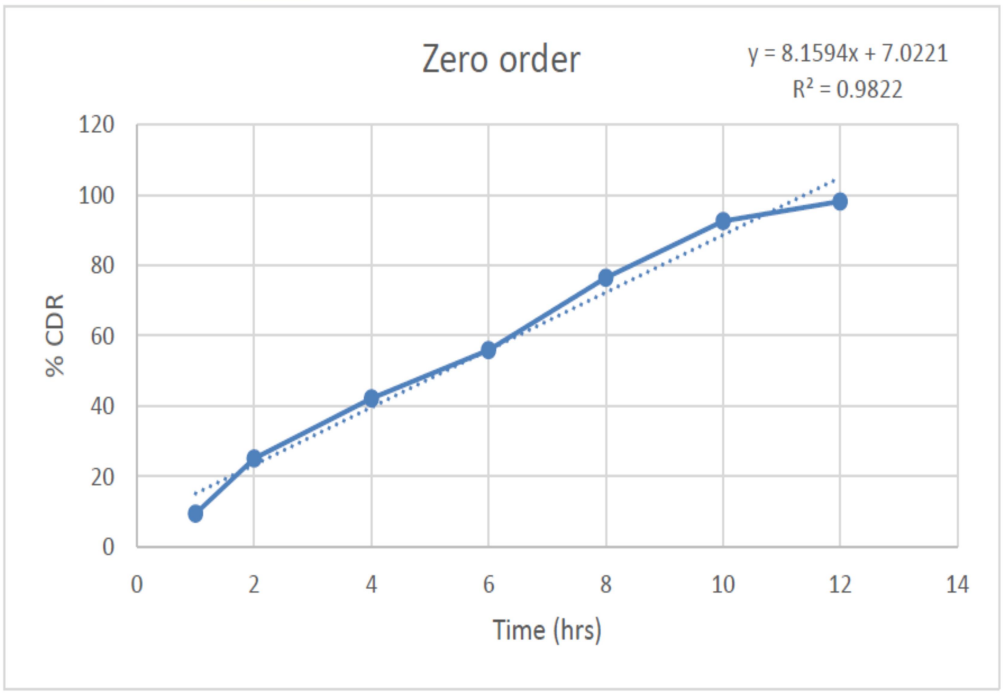

FIG. NO. 12: ZERO ORDER KINETIC STUDY

B. First order kinetic

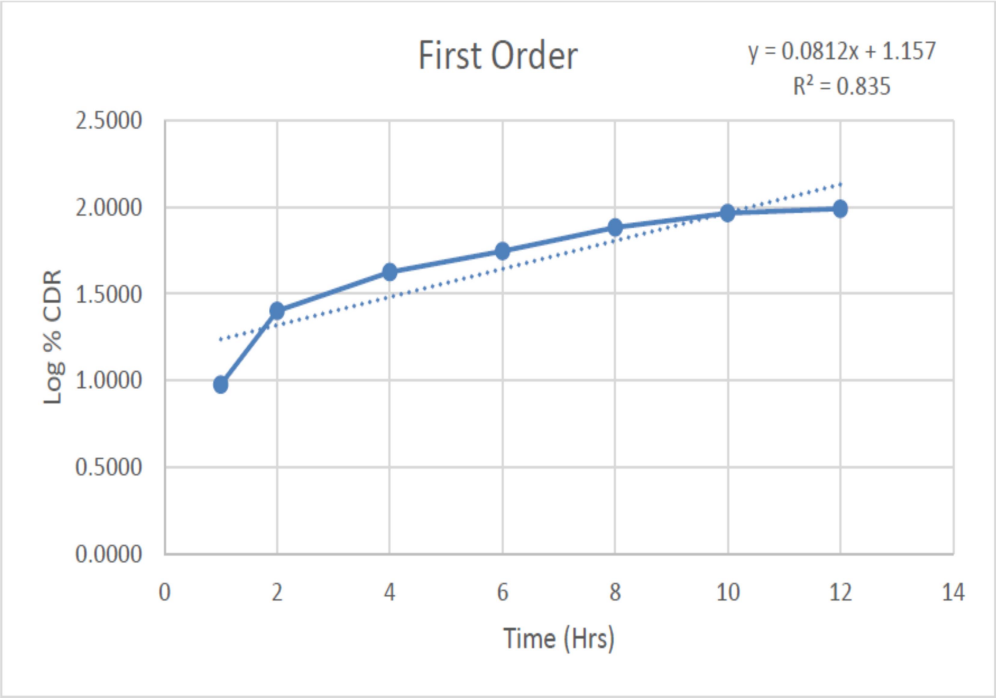

FIG. NO. 13: FIRST ORDER KINETIC STUDY

C. Higuchi equation

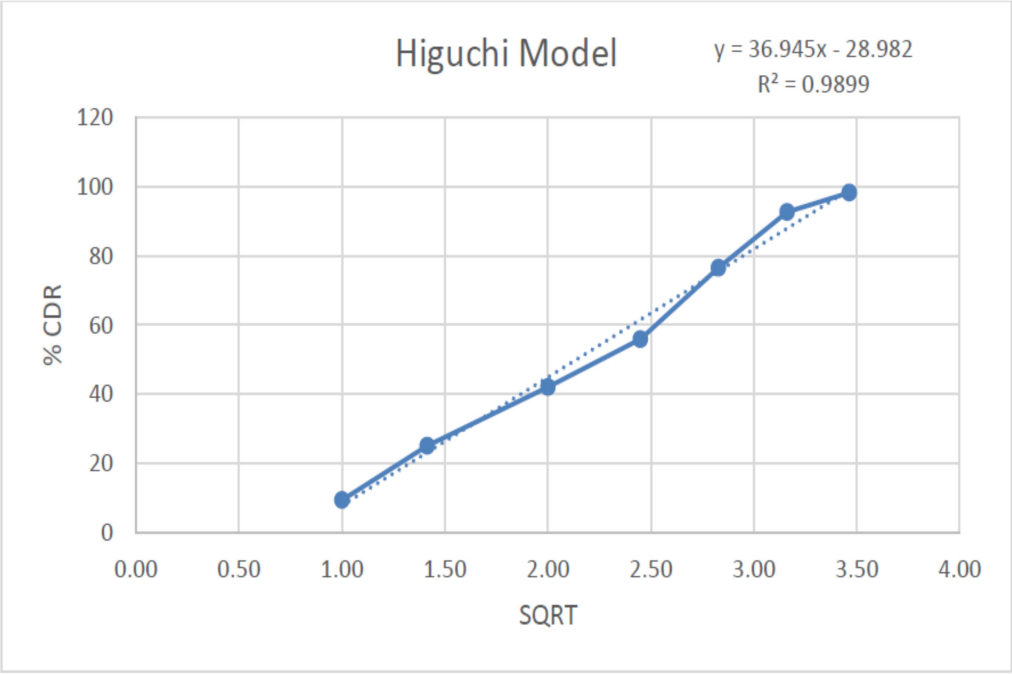

FIG. NO. 14: HIGUCHI PLOT

D. Korsemeyer-peppas equation

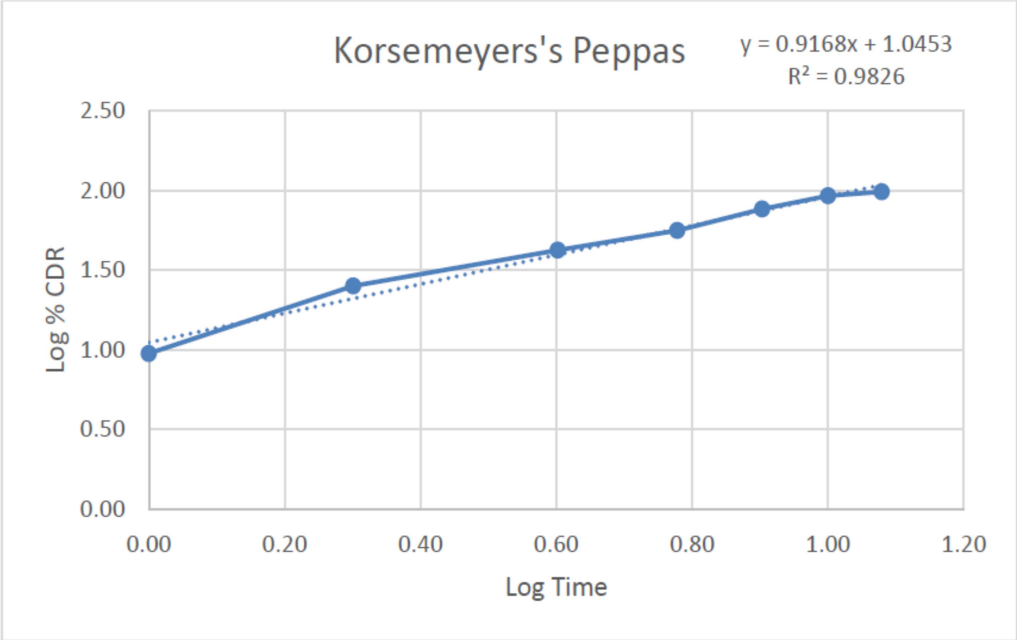

FIG. NO. 15: KORSEMEYER- PEPPAS PLOT

TABLE NO. 20: DRUG RELEASE BY USING DIFFERENT MODELS BY F4 BATCH

batch	kinetic model			
	Zero Order	First Order	Higuchi Model	Korsemeyer-peppas
F4	R^2	R^2	R^2	R^2
	0.9822	0.835	0.9899	0.9826

Stability study

The sample were withdrawn after 1, 2 and 3 months and subjected to followingtests as shown in Table. 21

TABLE NO. 21: DETAILS OF STABILITY STUDY FOR F4 BATCH

Test	Before	After		
	0 month	1 month	2 month	3 month
Drug release	98.16	98.06	97.68	97.24
Floating lag time	>12 hrs	>12hrs	>12hrs	>12hrs

The accelerated stability studies (carried for 3 months), at temperature of $40^0C \pm 2^0C$ and % RH 75% ± 5% RH indicated that the developed floating pectinate beads were unaffected after 03 months storage under accelerated condition as no change was observed in the appearance and colour of the formulation. On the basis of these results, it may be concluded that the optimized formulation developed is stable under accelerated condition of 03 months.

IV. SUMMARY AND CONCLUSION

Sodium alginate, carnauba wax and bees wax were selected for the preparation of floating alginate wax beads. The identity of Cilnidipine was confirmed by physical characteristics, spectrophotometric analysis such as Ultra violet visible spectrophotometric, Fourier Transform – Infra red and differential thermal colorimetic studies by preparing the floating alginate wax beads of Cilnidipine, the effect of different variables on floating alginate wax beads was studied. The prepared floating beads were evaluated for micromeritic properties, % drug contents, floating lag time, floating time, swelling index and % drug release in 0.1N Hydrochloric acid and its accelerated stability study.

The floating alginate wax beads containing Cilnidipine were prepared. The effect of various process and formulation variables on Cilnidipine floating beads were studied. The concentration of carnauba wax had significant effect on % drug release and floating lag time. However the drug release was greatly retarded as the concentration of carnauba wax increases and floating lag time was decreased.

After evaluation parameter of floating alginate wax beads, the best suited formulation (F4) was selected because of better floating lag time and sustained release of the drug. Formulation (F4) was evaluated for stability study, floating lag time, floating time and % drug release. The following conclusions can be drawn from present study:

a) Preformulation study of drug and polymers was done.
b) Compatibility study between drug and polymers was done by Fourier Transform Infrared spectrum analysis and it was found that there was no chemical interaction between drug and polymers.
c) Floating lag time of formulation was studied and it was found that as concentration of polymers increases the floating lag time also increases.
d) Surface characterization by Scanning Electron Microscopy of floating alginate wax beads was studied and it shown the uneven surface with spherical shape.
e) The sustained release rate and evaluation of prepared entrapped floating sodium alginate wax beads was studied.
f) The beads of optimized batch shown the bulk density as 0.361 ± 0.005, tapped density of 0.447 ± 0.025, Carr's index as 19.10 ± 5.34 and Hausner's ratio as 1.24 ± 0.08.
g) The beads of optimized batch shown the percentage yield as 98.20%, percentage drug content as 96.76 ± 0.07 %, percentage drug entrapment efficiency as 93.16 ± 0.59 %.
h) The optimized batch shown floating lag time of 1.27 min and floating time >12hr.
i) The F4 batch showed the maximum swelling index as 19.84 ± 0.03 and average particle size was found to be 1.12 ± 0.17.
j) The In vitro drug release study of different formulation was studied maximum drug release 98.16% was shown by optimized batch. After comparing the coefficient of regression (r2) values of different kinetic models, drug release kinetics for optimized floating beads best fitted in higuchi kinetic release.
k) No significant change was observed in present drug release before and after stability studies carried out for 03 months of batch (F4).
l) The characterization of different excipients in prepared floating alginate wax beads formulations was studied.

Thus it can be concluded that the floating wax beads can be a better approach for sustained release activity for drugs with short half life.

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VI. CONFLICTS OF INTEREST

Authors have no conflicts of interest to declare.

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