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Formulation and Evaluation of Dissolution enhanced Sustained Release Nifedipine capsule employing Lactose as a Hydrophilic diluent

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ABSTRACT

In order to produce a sustained release composition of a very low solubility drug, it is necessary to have one trait to increase the solubility and a second trait to slow down and control the rate of dissolution. Therefore, we exploited a hydrophobic polymer Ethyl Cellulose for sustained delivery of Nifedipine for the period of 12 hours and used lactose as a pore former in designing inert matrix of poorly soluble drug (Nifedipine). Five different formulations of nifedipine matrix granules with varying amounts of lactose (65, 58.33, 51.66, 45 and 38.33%) were prepared by wet granulation and the resultant granules were filled in size '2' hard gelatin capsules. The FT-IR spectra of the pure drug and formulation L3 indicated no chemical interactions between the drug and excipients used. The resultant granulations exhibited acceptable particle size distribution and good flow properties. Capsules prepared by using these granulations exhibited desirable pharmacotechnical properties. The average particle size of granules was found to be in the range of 500-841µm. The results of dissolution study of formulations L1, L2, L3, L4, L5 showed 84.77% in 6 hrs, 89.63% in 8 hrs, 89.57% in 12 hrs, 58.96% in 12 hrs and 52.14% in 12 hrs respectively. And therefore, formulation L3 with 51.66% Lactose was found to be most promising formulation as it showed sustained release (89.57%) as well as maintained excellent matrix integrity during the period of 12 hr study. The optimized formulation (L3) selected from the % drug release profiles was fitted into various kinetic models to know the mechanism of drug release from this formulation. The best fit release kinetic model was found to be Higuchi for L3, which indicated release of the drug by difussion from matrix type formulation. Drug release study supported the study hypothesis that as a result of formation of a nifedipine molecular dispersion, nifedipine dissolution inside the matrix was no longer the rate-limiting step for drug release, and the drug diffusion in matrix through the channels formed by dissolution of lactose became the slowest step instead. Indeed, the results offered formulation researcher a cheaper option that incurs no additional cost that may arise if a material is to be replaced because of the need to improve on response parameters such as dissolution and drug release. Therefore, it was also concluded that Lactose can be successfully used to modulate drug release of poorly water soluble drug Nifedipine in sustained release inert matrices.

Key words: *Nifedipine, Sustained – Release, Ethyl cellulose, Molecular dispersion, Enhanced solubility.*

INTRODUCTION

Oral drug delivery is the most chosen and suitable option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity, poor efficiency, repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems [1- 4]. Therefore, to maintain the concentration of drug in plasma within therapeutic index for effectual treatment and to surpass the limitations of conventional dosage forms, concomitant recognition of the therapeutic advantages of Sustained drug delivery came into existence [3] and greater attention is being paid on their development. But the major challenge these days is to increase the solubility of a low – solubility drugs along with the achievement of sustain release oral drug delivery system which avoids dose dumping [5, 3]. In order to produce a sustained release formulation of a drug having very low solubility in water, it is necessary to have one trait to increase the solubility and a second trait to slow down and control the rate of release. Nifedipine (CCB) was chosen as a choice of drug because of its complete drug absorption over the entire gastrointestinal tract, despite drawbacks like poor solubility in water, biological half – life of 2 to 4 hrs. , further it is rapidly metabolized and excreted, lacks to maintain its concentration at the site of action and hence shows irregular bioavailability upon oral administration. The task of increasing the solubility and providing a sustained-release nifedipine formulation was accomplished by preparing adequate ethyl cellulose matrix granules comprising lactose as a channeling agent by wet granulation to provide a predetermined dose or number of doses of nifedipine. Each of the supposed granules [6] having a diameter between 0.5 and 2.5 mm [7] was filled into hard shell gelatin capsule.

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MATERIALS AND METHOD

Chemicals and Reagents:

Nifedipine was procured from Suchem Laboratories, Ahemdabad, Ethyl cellulose was supplied by CDH (P) Ltd, New Delhi and other ingredients used like lactose, dichloro methane, ethanol, maize starch, talc, etc were of analytical grade.

Pre-Formulation Studies:

Physical description **-** In evaluating the physical properties of the Nifedipine, its colour was observed.

Identification of the drug:

☞ Infrared red spectroscopy (FTIR-8400) - The infrared spectra of the procured samples were obtained on a Fourier transform Infrared spectrophotometer [(FTIR-8400) Shimadzu, Japan] in order to identify them by comparing their spectra with that of the respective reference standards.

Procedure: The samples were first ground gently in a mortar and mixed with KBr in the ratio of 1:10. Scans were obtained at a resolution of 2 cm^{-1}, over a frequency range of 4000 to 400 cm^{-1} [8].

Loss on Drying (at 105 °C) for 2 hrs: This parameter was tested to calculate the moisture content of the samples.

Procedure: 1 gm of the sample was weighed accurately. A glass-stoppered shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination was tared. The test specimen was put in the bottle, the cover was replaced and the bottle and the contents were weighed accurately. The loaded bottle was placed in the drying chamber (LOD Oven) by removing the stopper and leaving it also in the chamber. The test specimen was dried at 105 °C and for 2 hrs [9].
Note: Upon opening the chamber close the bottle promptly and allow it to come to room temperature in a dessicator before weighing.

Calculation

$$\% \text{ Loss on drying} = \frac{W2 - W3}{W2 - W1} \times 100$$

Where,
W1 = Weight of the empty bottle in grams.
W2 = Weight of the bottle with sample in grams (Before drying)
W3 = Weight of the bottle with sample in grams. (After drying) – As time specified.

Physico-chemical Properties:

☞ *Melting point:*

The sample was loaded into a sealed capillary and heated electrically via a heating block controlled by a digital temperature controller. Samples in capillaries were inserted from the top and observed from the eyepiece which has a magnifier. And the melting temperature range of the sample was recorded by recording the thermometer reading [10].

☞ *Solubility:*

Different solvents were prepared according to the procedure given in I.P. Procedure: Drug was added in excess in 3 ml of each solvent (acetone, methylene chloride, chloroform, ethyl acetate, methanol, ethanol and water in separate test tubes .The test tubes were kept in ultrasonicator for 15 minutes and on mechanical shaker for 6 hrs. for equilibration. After 6 hrs. contents of each test tube were filtered, suitably diluted and analysed for the drug content using UV spectroscopy [11].

☞ *Flow Properties:*

Bulk density: Apparent bulk density was determined by placing pre-sieved samples in to a graduated cylinder and measuring the volume and weight as it is.

Bulk density = weight of powder/ volume of powder

Tapped density: Tapped density was determined by USP method II. Sample was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula:

Tapped density = weight of powder/ tapped volume of packing

Angle of Repose: Angle of repose of the samples was determined by the funnel method (Reposgram). A funnel was fixed to a desired height and the sample was filled in it. It was allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula,

$$\tan \theta = D / 2h$$

Where, h and D are height and diameter of the pile respectively.

Table No. 1: Flow of Powders with Angle of Repose values

Angle of repose (degrees)	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable*
> 40	Very poor

*May be improved by glidant

☞ *Partition coefficient:*

Partition coefficient of nifedipine was determined at 37 ± 0.5 °C by taking 10 ml of octanol which was saturated with 10 ml of phosphate buffer (pH7.2) by shaking with externally driven magnetic stirrer. After shaking the system remained undisturbed for half an hour. About 10 mg of drug was added to this solution and was shaken on wrist action mechanical stirrer. Two layers were separate through separating funnel and filterer through Whatman grade filter, and the amount of nifedipine solubilized, was determined by measuring the absorbance at 338 nm against reagent blank through double beam UV/Vis spectrophotometer (Shimadzu) in both the solution. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in phosphate buffer (pH 7.2) and the value were reported as log P.

$$K_{o/w} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}}$$

Drug- excipient compatibility study: Fourier Transform Infrared Spectroscopy (FT-IR):

FT-IR spectroscopy was carried out to check the compatibility between the drug, polymer and lactose. FTIR, was performed onsamples of nifedipinepure drug (A), solid admixture of nifedipie, ethylcellulose (B)andlactose (C). The IR Spectra of the test samples were obtained using KBr diskmethod.

Procedure: For this the samples were first ground gently in a mortar and mixed with KBr in the ratio of 1:10. Scans were obtained at a resolution of 2 cm^{-1}, over a frequency range of 4000 to 400 cm^{-1} [12, 13].

Formulation Design:

Table No. 2: Formulation ingredients

Material	Use
Nifedipine	Drug
Ethyl cellulose	Matrix polymer
Lactose	Hydrophillic diluent
Maize starch	Binder
Ethanol	Solvent
Dichloro methane	Solvent
Talc	Glidant

Five different formulations of nifedipine matrix granules with varying amounts of lactose (65, 58.33, 51.66, 45 and 38.33%) and the remaining quantity was compensated by polymer concentration (Table 3). Granules were prepared by wet granulation method and the resultant granules were filled in size '2' hard gelatin capsules.

Table No. 3: Composition of Sustained Release Nifedipine Granules

Ingredients	Formulation Code				
	F1	F2	F3	F4	F5
Nifedipine (mg)	20	20	20	20	20
Ethyl cellulose (mg)	20	40	60	80	100
Lactose (mg)	**195**	**175**	**155**	**135**	**115**
Dichloro methane	q.s.	q.s.	q.s.	q.s.	q.s.
Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.
Maize Starch (mg)	60	60	60	60	60
Sun set yellow (mg)	0.15	0.15	0.15	0.15	0.15
Talc (mg)	5	5	5	5	5
Total weight (mg)	300	300	300	300	300

Preparation of Granules:

Step 1: Dry powder screening and blending- All the ingredients were weighed accurately according to the formulation batch and passed through a 35-mesh sieve. Nifedipine (active ingredient), ethyl cellulose (polymer) and lactose (filler) were mixed in a cubic mixer (Erweka, Germany).

Step 2: Granule preparation

The powder blends were granulated using a Glatt GPCG-3 fluid bed (Glatt Air Techniques, USA). To the powder blend (nifedipine, lactose and ethyl cellulose) was added a binder solution of maize starch dissolved in ethanol-dichloro methane in the ratio of 1:1 v/v q.s. The resulting granules were dried in the Glatt at 40ºC for 30 minutes.

Step 3 : Dry Sifting – The dried granules were made to pass through sieve 20# and 30# mesh and granules retained on 30# mesh were collected.

Filling of Capsules:

The collected granules were filled into size "2" hard gelatin capsules to obtain 20 mg Nifedipine / capsule.

Evaluation Study of Blend:

Description: The blend was physically checked for colour, uniformity of blending, absence of lumps and foreign particles.

Loss on Drying (at 105 ˚C) for 2 hrs – To calculate the moisture content of the blend, 1 gm of the blend was weighed accurately. A glass-stoppered shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination was tared. The blend was put in the bottle, the cover was replaced and the bottle and the contents were weighed accurately. The loaded bottle was placed in the drying chamber (LOD Oven) by removing the stopper and leaving it also in the chamber. The blend was dried at 105 °C and for 2 hrs [9].

Calculation

$$\% \text{ Loss on drying} = \frac{W2 - W3}{W2 - W1} \times 100$$

Where,
W1 = Weight of the empty bottle in grams.
W2 = Weight of the bottle with blend in grams(Before drying)
W3 = Weight of the bottle with blend in grams. (After drying)

Bulk density: Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is.

Bulk density = weight of blend/ volume of blend

Tapped density: Tapped density was determined by USP method II. The blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula

Tapped density = weight of blend/ tapped volume of packing

Angle of Repose: Angle of repose of the blend was determined by the height cone method. A funnel was fixed to a desired height and the blend was filled in it. It was allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula,

$$\tan \theta = D/2h$$

Where, h and D are height and diameter of the pile respectively.

Blend Uniformity: Blend uniformity was determined to confirm the uniform mixing of the active ingredient (nifedipine) in the blend.

Standard preparation: Accurately weighed 50 mg nifedipine working standard was transferred in 100 ml volumetric flask. To it 50 ml methanol was added and From the above solution, 2 ml of the solution was pipette out into 25ml volumetric flask and the volume was made up by methanol.

Sample Preparation: Accurately weighed 600 mg (equivalent to 2 dosage units) was taken and dissolved in 20ml of methanol using a 100ml volumetric flash. This was sonicated for about 10 min or more until a clear solution is obtained. The flask was then made up to volume with more methanol, and the solution was filtered through what man No. 1 filter paper. 5ml of the filtrate was again taken & diluted to 50ml with methanol. Similarly 9 other samples were prepared.

Procedure: The standard and sample preparations were filtered through Whatman filter paper grade 1 at each step and the absorbance was read at 350 nm on Ultra – violet spectrophotometer using methanol as blank.

Calculation:

$$\% \text{ Nifedipine} = \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{2}{25} \times \frac{100}{W_T} \times \frac{50}{5} \times \frac{P}{100} \times \frac{100}{20} \times 1$$

Where, A_T = Absorbance of sample preparation
A_S = Absorbance of standard preparation
W_T = Weight of sample preparation
W_S = Weight of standard preparation
P = Potency of nifedipine working standard

Dissolution (Nifedipine) by UV:

Chemicals and Reagents Required: Potassium dihydrogen phosphate, sodium hydroxide, potassium chloride, concentrated hydrochloric acid, potassium bipthalate and polysorbate 80.

Preparation of Buffer pH 1.2 (HCl – KCl) : Accurately weighed 14.9 g of potassium chloride was dissolved in 500 ml water, to which 13 ml of concentrated HCl was added and the prepared solution was diluted to 4 lt with water. The pH of the solution was checked and it should be 1.2 ± 0.2. 4 g of polysorbate 80 was dissolved in the buffer.

Preparation of Potassium Bipthalate Buffer pH 7.2: Accurately weighed 40.84 g of potassium bipthalate was dissolved in 500 ml water, to which 60 ml of 0.2 M sodium hydroxide was added and the prepared solution was diluted to 4 lt with water. The pH of the solution was checked and it should be 4.2 ±0.2. 4 g of polysorbate 80 was dissolved in the buffer.

Preparation of Phosphate Buffer pH 4.2: Accurately weighed 27.2 g of potassium dihydrogen phosphate was dissolved in 500 ml water, to which 60 ml of 0.2 M sodium hydroxide was added and the prepared solution was diluted to 4 lt with water. The pH of the solution was checked and it should be 7.2 ± 0.2. 4 g of polysorbate 80 was dissolved in the buffer.

Standard preparation: Accurately weighed 50 mg nifedipine working standard was transferred in 100 ml volumetric flask. To it 50 ml methanol was added and sonicated to dissolve, and the remaining volume was made up with methanol. From the above solution, 2 ml of the solution was pipette out into 100 ml of the respective buffers (ph1.2, 4.2 and 7.2) and filterd through whatman filter paper grade 1.

Sample preparation: 300 mg of blend sample was placed in each of the six dissolution vessels containing 500 ml of the dissolution medium of buffer ph 1.2, dissolution parameters were set and process was started. After 2 hrs, 10 ml aliquot was withdrawn from each jar and the whole buffer solution was filtered through Whatman filter paper grade 1. The residue left over the filter papers were transferred into respective empty six vessels which were refilled by 500 ml of pH 4.2 buffer and the instrument was again started for 1 hour. After completion of 1 hr, 10 ml aliquot was withdrawn from each jar and the buffer solutions were filtered through Whatman filter paper grade 1. The residue left over was transferred into respective vessels which were refilled by 500 ml of pH 7.2 buffer and the instrument was restarted for 3 hour. After completion of 3 hrs, 10 ml aliquot was withdrawn from each jar and simultaneously 10 ml of fresh buffer was added to each jar and the instrument was run again for 2 hrs. After completion of 2 hrs, 10 ml aliquot was withdrawn from each jar and simultaneously 10 ml of fresh buffer was added to each jar and the instrument was run again for 4 hrs. . After 4 hrs, 10 ml aliquot was withdrawn from each jar.

Procedure: The study was performed in USP drug release apparatus II Paddle type (Electrolab TDT 06L) in various release media i.e. simulated gastric fluid of pH 1.2 for 1st hour, mixture of simulated gastric and intestinal fluid of pH 4.2 for 2nd and 3rd hours and simulated intestinal fluid of pH 7.2 for subsequent hours (12 hrs.). The rotation speed of paddle was kept at 50 rpm, and the temperature was maintained at 37.5 ± 0.5 °C.300 mg blend was inserted in each assembly At pre determined time intervals, 10 ml

aliquots were withdrawn and analyzed by UV-.Vissible spectrophotometer (UV 1601 PC, Shimadzu Scientific Instruments, Columbia, MD, USA) at a wavelength of 338 nm. using respective dissolution medias as blank.

Table No. 4: Process Parameters

Medium	Buffer
Volume	500 ml
Apparatus	USP Apparatus II
Speed	50 r.p.m
Time	12 hrs.
Temperature	37 ± 0.5 ° C
Sampling interval	2, 3, 6, 8 and 12 hrs.

Calculation:

$$\% \text{ Drug release} = \frac{AT}{AS} X \frac{WS}{100} X \frac{2}{100} X \frac{500}{WT} X \frac{P}{100} X \frac{100}{20} X 1$$

Where, A_T = Absorbance of sample preparation
A_S = Absorbance of standard preparation
W_T = Weight of sample preparation
W_S = Weight of standard preparation
P = Potency of nifedipine working standard

Drug and excipients interaction study:- Fourier Transform Infrared Spectroscopy (FT-IR)

The infrared spectra of the nifedipine, ethyl cellulose, lactose and the physical mixture were obtained on a Fourier transform Infrared spectrophotometer [(FTIR-8400) Shimadzu, Japan] in order to detect the existence of interactions between nifedipine and hydrophobic or hydrophilic excipients in the granulation.

Procedure: The samples were first ground gently in a mortar and mixed with KBr before being formulated into granules. Scans were obtained at a resolution of 2 cm^{-1}, over a frequency range of 4000 to 400 cm^{-1}.

Assay: By UV Spectroscopy

Standard preparation: Accurately weighed 50 mg nifedipine working standard was transferred in 100 ml volumetric flask. To it 50 ml methanol was added and sonicated to dissolve, and the remaining volume was made up with methanol. From the above solution, 2 ml of the solution was taken in 25 ml volumetric flask making up the volume with methanol and the solution was filterd through whatman filter paper grade 1.

Sample Preparation: Accurately weighed 300 mg of the blend was taken and dissolved in 20ml of methanol using a 50ml volumetric flash. This was shaken vigorously for about 15Min or more until a clear solution is obtained. The flask was then made up to volume with more methanol, and the solution was filtered through what man No. 1 filter paper. 5ml of the filtrate was again taken & diluted to 50ml with methanol.

Procedure: The standard and sample preparations were filtered through Whatman filter paper grade 1 at each step and the absorbance was read at 350 nm on Ultra – violet spectrophotometer using methanol as blank.

Calculation:
Nifedipine (mg/300 mg blend)

$$= \frac{AT}{AS} X \frac{WS}{100} X \frac{2}{25} X \frac{50}{WT} X \frac{50}{5} X \frac{P}{100} X \frac{100}{20} X 1$$

$$\% \text{ Nifedipine} = \frac{\text{mg/300 mg blend}}{20} X 100$$

Where, A_T = Absorbance of sample preparation
A_S = Absorbance of standard preparation
W_T = Weight of sample preparation
W_S = Weight of standard preparation
P = Potency of nifedipine working standard

Evaluation Study of the Finished Product (Capsule):
Description: Randomly selected 10 capsules were unlocked and their contents were placed on a white sheet of paper and observed for the nature of filled material and colour.

Uniformity of Weight: 20 capsules were randomly selected from each batch, weighed indivdually and thereafter their average weight was calculated. Not more than two of the individual weights should deviate from the average weight by ± 7.5% and none should deviate from ± 15.0%. The maximum and the minimum deviation were calculated using the following formula :

Maximum Deviation =
$$\frac{\text{max. weight – avg. weight of twenty capsules}}{\text{avg. weight of twenty capsules}} X 100$$

Minimum deviation =
$$\frac{\text{min. weight – avg. weight of twenty capsules}}{\text{avg. weight of twenty capsules}} X 100$$

Uniformity of Net Content: 20 capsules were randomly selected from each batch and unlocked one by one to record the filled content weight individually and thereafter their average weight was calculated. Not more than two of the individual weights should deviate from the average weight by ± 7.5% and none should deviate from ± 15.0%.

Maximum Deviation =
$$\frac{\text{max. net content – avg. net content of twenty capsules}}{\text{avg. net content of twenty capsules}} X 100$$

Minimum deviation =
$$\frac{\text{min. net content – avg. net content of twenty capsules}}{\text{avg. net content of twenty capsules}} X 100$$

Flow Properties of granules:
Bulk density: Apparent bulk density was determined by placing pre-weighed granules in to a graduated cylinder and measuring the volume and weight as it is.

Bulk density = weight of granules/ poured volume of powder

Tapped density: Tapped density was determined by USP method II. Pre-weighed granules were filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the granular bed volume has reached a minimum, thus was calculated by formula:

Tapped density = weight of granules/ tapped volume of packing

Angle of Repose: Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height and the granules were filled in it. It was allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula,

$$\tan \theta = D/2h$$

Where, h and D are height and diameter of the pile respectively.

Carr's Index: Percentage compressibility or Carr's index (CI) is based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

Carr's index (%) = poured density-tapped density/ poured densityX100

Table No. 5: Flow of Powders with Carr's Index values

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable*
23-35	Poor
33-38	Very poor
> 40	Extremely poor

*May be improved by glidant

Hausner's ratio: Hausner's ratio was calculated using the formula,

$$\text{Hausner's ratio} = \frac{\text{poured density}}{\text{tapped density}}$$

Table No. 6: Flow of Powders with Hausner's Ratio values

Values	Comments
Less than 1.25	Good flow
Greater than 1.5	Poor flow
Between 1.25-1.5	Addition of glidant normally improves the flow

Particle size distribution (% Retained):

Dry Sieving Method was applied to analyze the particle size distribution. For this analysis nested column of 20#, 30#, 35#, 40# and 60# mesh sieves was taken and placed in a mechanical shaker . The sieves were arranged in the ascending order to obtain coarest sieve on the top and each lower sieve in the column had smaller openings than the one above. An accurately weighed ammount of granules (50 mg) were poured into the top sieve which has the largest screen openings. The shaker was put on for 10 min and after the shaking was complete the material on each sieve was weighed to calculate the % Retained.

$$\% \text{ Retained} = \frac{W \text{ Seived}}{W \text{ Total}} \times 100$$

Where, W_{Sieve} is the weight of aggregate in the sieve and W_{Total} is the total weight of the aggregate.

Drug - Excipient Compatibility Study : Fourier Transform Infrared Spectroscopy (FT-IR):

The infrared spectra of the nifedipine, ethyl cellulose, lactose and the prepared granules were obtained on a Fourier transform Infrared spectrophotometer [(FTIR-8400) Shimadzu, Japan] in order to detect the existence of interactions between nifedipine and hydrophobic or hydrophilic excipients in the granulation.

Procedure: The samples were first ground gently in a mortar and mixed with KBr. Scans were obtained at a resolution of 2 cm^{-1}, over a frequency range of 4000 to 400 cm^{-1} and compared with that of standards

Drug content:

Standard preparation: Accurately weighed 50 mg nifedipine working standard was transferred in 100 ml volumetric flask. To it 50 ml methanol was added and sonicated to dissolve, and the remaining volume was made up with methanol. From the above solution, 2 ml of the solution was pipette out into 25ml volumetric flask and the volume was made up by methanol.

Sample Preparation: One capsule was randomly selected and unlocked and the granules were crushed and powdered, using a mortal & pestle. The amount of this finely powder granules equivalent to 20mg of Nifedipine was taken and dissolved in 50ml of methanol using a 100ml volumetric flash. This was shaken vigorously for about 15Min or more until a clear solution is obtained. The flask was then made up to volume with more methanol, and the solution was filtered through what man No. 1 filter paper. 5ml of the filtrate was again taken & diluted to 50ml with methanol. Similarly 9 other samples were prepared.

Procedure: The standard and sample preparations were filtered through Whatman filter paper grade 1 at each step and the absorbance was read at 350 nm on Ultra – violet spectrophotometer using methanol as blank.

Calculation:

$$\% \text{ Nifedipine} = \frac{A_T}{A_S} X \frac{W_S}{100} X \frac{2}{25} X \frac{100}{W_T} X \frac{50}{5} X \frac{P}{100} X \frac{100}{20} X 1$$

Where, A_T = Absorbance of sample preparation
A_S = Absorbance of standard preparation
W_T = Weight of sample preparation
W_S = Weight of standard preparation
P = Potency of nifedipine working standard

Assay: By UV Spectroscopy

Standard preparation: Accurately weighed 50 mg nifedipine working standard was transferred in 100 ml volumetric flask. To it 50 ml methanol was added and sonicated to dissolve, and the remaining volume was made up with methanol. From the above solution, 2 ml of the solution was taken in 25 ml volumetric flask making up the volume with methanol and the solution was filterd through whatman filter paper grade 1.

Sample Preparation: Twenty capsules were randomly selected and unlocked and the granules were crushed and powdered, using a mortal & pestle. The amount of this finely powder granules equivalent to 20mg of Nifedipine was taken and dissolved in 20ml of methanol using a 50ml volumetric flash. This was shaken vigorously for about 15Min or more until a clear solution is obtained. The flask was then made up to volume with more methanol, and the solution was filtered through what man No. 1 filter paper. 5ml of the filtrate was again taken & diluted to 50ml with methanol.

Procedure: The standard and sample preparations were filtered through Whatman filter paper grade 1 at each step and the absorbance was read at 350 nm on Ultra – violet spectrophotometer using methanol as blank.

Calculation:

Nifedipine (mg/capsule)

$$= \frac{A_T}{A_S} X \frac{W_S}{100} X \frac{2}{25} X \frac{50}{W_T} X \frac{50}{5} X \frac{P}{100} X \frac{100}{20} X 1$$

$$\% \text{ Nifedipine} = \frac{\text{mg/capsule}}{20} X \frac{100}{}$$

Where, A_T = Absorbance of sample preparation
A_S = Absorbance of standard preparation
W_T = Weight of sample preparation
W_S = Weight of standard preparation
P = Potency of nifedipine working standard

In – vitro Drug Release:

Preparation of Buffer pH 1.2 (HCl – KCl) : Accurately weighed 14.9 g of potassium chloride was dissolved in 500 ml water, to which 13 ml of concentrated HCl was added and the prepared solution was diluted to 4 lt with water. The pH of the solution was checked and it should be 1.2 ± 0.2. 4 g of polysorbate 80 was dissolved in the buffer.

Preparation of Potassium Bipthalate Buffer pH 7.2: Accurately weighed 40.84 g of potassium bipthalate was dissolved in 500 ml water, to which 60 ml of 0.2 M sodium hydroxide was added and the prepared solution was diluted to 4 lt with water. The pH of the solution was checked and it should be 4.2 ±0.2. 4 g of polysorbate 80 was dissolved in the buffer.

Preparation of Phosphate Buffer pH 4.2 : Accurately weighed 27.2 g of potassium dihydrogen phosphate was dissolved in 500 ml water, to which 60 ml of 0.2 M sodium hydroxide was added and the prepared solution was diluted to 4 lt with water. The pH of the solution was checked and it should be 7.2 ± 0.2. 4 g of polysorbate 80 was dissolved in the buffer.

Standard preparation: Accurately weighed 50 mg nifedipine working standard was transferred in 100 ml volumetric flask. To it 50 ml methanol was added and sonicated to dissolve, and the remaining volume was made up with methanol. From the above solution, 2 ml of the solution was pipette out into 100 ml of the respective buffers (ph1.2, 4.2 and 7.2) and filterd through whatman filter paper grade 1.

Sample preparation: One unit was placed in each of the six dissolution vessels containing 500 ml of the dissolution medium of buffer ph 1.2, dissolution parameters were set and process was started. After 2 hrs, 10 ml aliquot was withdrawn from each jar and the whole buffer solution was filtered through Whatman filter paper grade 1. The residue left over the filter papers were transferred into respective empty six vessels which were refilled by 500 ml of pH 4.2 buffer and the instrument was again started for 1 hour. After completion of 1 hr, 10 ml aliquot was withdrawn from each jar and the buffer solutions were filtered through Whatman filter paper grade 1. The residue left over was transferred into respective vessels which were refilled by 500 ml of pH 7.2 buffer and the instrument was restarted for 3 hour. After completion of 3 hrs, 10

ml aliquot was withdrawn from each jar and simultaneously 10 ml of fresh buffer was added to each jar and the instrument was run again for 2 hrs. After completion of 2 hrs, 10 ml aliquot was withdrawn from each jar and simultaneously 10 ml of fresh buffer was added to each jar and the instrument was run again for 4 hrs. . After 4 hrs, 10 ml aliquot was withdrawn from each jar.

Procedure: The study was performed in USP drug release apparatus II Paddle type (Electrolab TDT 06L) in various release media i.e. simulated gastric fluid of pH 1.2 for 1st hour, mixture of simulated gastric and intestinal fluid of pH 4.2 for 2nd and 3rd hours and simulated intestinal fluid of pH 7.2 for subsequent hours (12 hrs.). The rotation speed of paddle was kept at 50 rpm, and the temperature was maintained at 37.5 ± 0.5 ˚C. Single unit was inserted in each assembly at pre determined time intervals, 10 ml aliquots were withdrawn and analyzed by UV-.Vissible spectrophotometer (UV 1601 PC, Shimadzu Scientific Instruments, Columbia, MD, USA) at a wavelength of 338 nm. using respective dissolution medias as blank.

Table No. 7: Process Parameters

Medium	**Buffer**
Volume	500 ml
Apparatus	USP Apparatus II
Speed	50 r.p.m
Time	12 hrs.
Temperature	37 ± 0.5 ° C
Sampling interval	2, 3, 6, 8 and 12 hrs.

Calculation:

$$\% \text{ Drug release} = \frac{AT}{AS} X \frac{WS}{100} X \frac{P}{100} X \frac{500}{WT} X \frac{P}{100} X \frac{100}{20} X 1$$

Where, A_T = Absorbance of sample preparation
A_S = Absorbance of standard preparation
W_T = Weight of sample preparation
W_S = Weight of standard preparation
P = Potency of nifedipine working standard

Determination of release kinetics: To analyze the mechanism of release and release rate kinetics of the formulation, the data obtained were fitted into Zero order, First order, Higuchi matrix, and Peppa's model. Based on the r-value, the best-fit model was selected.

RESULT AND DISCUSSION

The present work was aimed at exploitation of hydrophilic diluents Lctose for enhancing the solubility of Nifedipine, further, at achieving sustained release for the period of 12 hours. Preformulation studies of the procured samples using physicomechanical tests (Table-8) enabled identification of the samples; as well as FT-IR spectra of the drug and physical mixture of drug and the excipients showed no interaction as shown in **Fig, 1 .**

Table No. 8: Physico-Chemical Parameters of Procured Samples

Sr. No.	Sample	M.P° C ± S. D	Solubility (mg/ml)		B.D (g/cm³) ± S. D	T.D(g/cm³) ± S. D
			DCM ± S. D	Ethanol ± S. D		
1	Nifedipine	173± 0.56	160± 0.42	17± 0.56	1.45± 0.01	1.53± 0.01
2	Ethyl Cellulose	248± 0.27	115.8±0.19	14.5±0.56	1.69± 0.10	1.85± 0.12
3	Lactose	202.8±0.11	108.4±0.14	103.3±0.4	1.53± 0.02	1.61± 0.03

M. P – Melting Point; D C M – Dichloromethane; B. D – Bulk Density; T. D – Tapped Density; Each value represents the mean ± standard deviation

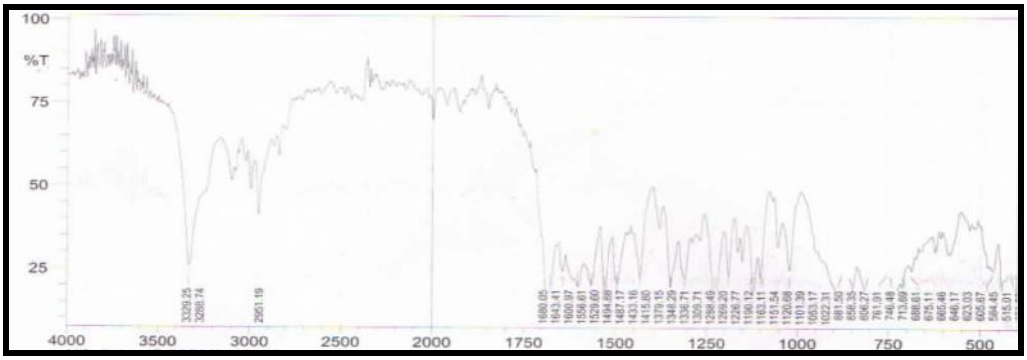

Fig. 1: Infrared Spectra of Nifedipine and Excipients mixture

Preliminary characterization of the blend was done by evaluating it for bulk density, tapp density, angle of repose and carr's index. The evaluated parameters were within acceptable range. The values are indicated in (Table-9). Blend uniformity and assay indicated that the drug was uniformly mixed with the excipients and 300 mg of the blend contained 20 mg of nifedipine, as required.

Table No. 9: Evaluation of the Blend

Sr. No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (degree)	C. I.%
1	0.31±0.01	0.42 ± 0.10	20.72±0.15	14.47±0.21

Each value represents the mean ± standard deviation, n=6

The prepared capsules were subjected to preliminary characterization such as uniformity of weight and uniformity of drug content and the evaluated parameters were within acceptable range for all the five formulations (Table 10).

Table No. 10: Uniformity of Weight & Net Content

Formulation	Average Weight ± S. D	Average Net Content ± S. D
L_1	299.47 ± 0.56	300.45 ± 0.77
L_2	301.71 ± 0.82	299.97 ± 0.54
L_3	300.06 ± 0.46	300.12 ± 0.19
L_4	299.94 ± 0.68	289.65 ± 0.95
L_5	299.42 ± 0.42	301.03 ± 0.77

Each value represents the mean ± standard deviation

Granules of all the five formulations were also evaluated for physicochemical parameters bulk density, tapped density, angle of repose, Carr's index and Hausner's number. The bulk density and tapped density of various formulations ranged from 0.37 – 0.60 g/ml and 0.40 – 0.71 g/ml respectively.The granules showed acceptable angle of repose ranged between 19.65° and 24.99°, low Carr's index values (14.47 – 20.46 %) indicating good-fair flow properties. Also the granules showed acceptable Hausner's ratio ranged from 0.96 – 1.23. (Table-11 and Figure 2)

Table No. 11: F_1 - F_5 Physical Parameters

Formulation	Bulk Density ± S.D.(g/ml)	Tapped Density ± S.D. (g/ml)	Angle of Repose ± S.D. (degree)	C. I ± S.D. %	Hausner's Ratio ±S.D.
L_1	0.37±0.001	0.40 ± 0.01	19.65 ± 0.21	16.88±0.61	0.96±0.03
L_2	0.41±0.010	0.46 ± 0.001	21.55±0.11	13.93±0.37	1.06±0.01
L_3	0.39±0.01	0.42 ± 0.10	20.72±0.15	14.47±0.21	1.03±0.001
L_4	0.54±0.001	0.60 ± 0.002	24.99±0.17	20.46±0.41	1.21±0.01
L_5	0.60±0.010	0.71 ± 0.10	23.81±0.21	19.98±0.51	1.23±0.001

Each value represents the mean ± standard deviation

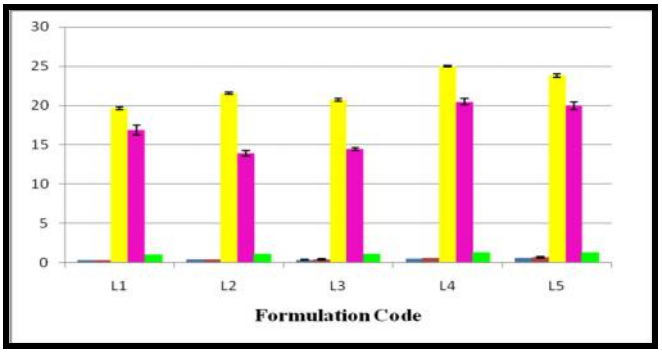

Fig. 2: Physical Parameters of Various Formulations

The particle size distributions of granules are shown in (Table 12 and Figure 3) which depicts the granule size range within 800 – 500 um.

Table No. 12: Particle Size Distribution of Various Formulations

Sieve no.	Size (mm)	Size (µm)	% Retained				
			L_1± S. D	L_2± S. D	L_3± S. D	L_4± S. D	L_5± S. D
20	0.841	841	0.30±0.02	0.17±0.12	0.2±0.10	0.31±0.11	0.26±0.10
30	0.6	600	74.19±0.1	75.21±0.1	75.06±0.1	70.98±0.1	73.56±0.1
35	0.50	500	24.65±0.1	23.73±0.1	24.09±0.1	27.54±0.1	24.75±0.1
40	0.400	400	0.49±0.21	0.89±0.11	0.65±0.12	1.11±0.10	1.43±0.12
60	0.250	250	0.37±0.10	-	-	0.06±0.11	-

Each value represents the mean ± standard deviation

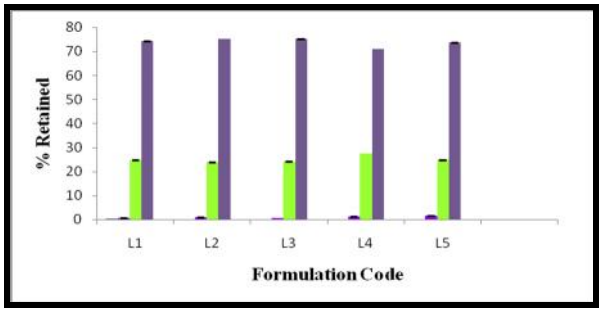

Fig. 3: Particle size distribution of Various Formulations

The FT-IR spectra of the pure drug and formulation F3 indicated that characteristics peaks of Nifedipine were not altered without any change in their position after successful entrapment in the matrix, indicating no chemical interactions between the drug and carrier used. The percentage drug content for different granular formulations indicated the uniformity in drug content as shown in (Table – 13).

Table No. 13: F_1 - F_5 % Drug Content

Sr. No.	Formulation Code	% Drug Content ± S.D
1	L_1	98.72 ± 0.10
2	L_2	100.05 ± 0.01
3	L_3	99.83 ± 0.01
4	L_4	97.08 ± 0.10
5	L_5	101.12+ 0.02

Each value represents the mean ± standard deviation

Assay for the optimized formulation (F_3) confirmed the presence of 99.74% of the nifedipine in each capsule, which was within the permissible limits of the label claim.

The results of dissolution study of formulations F1, F2, F3, F4, F5 showed 84.77% in 6 hrs, 89.63% in 8 hrs, 89.57% in 12 hrs, 58.96% in 12 hrs and 52.14% in 12 hrs respectively (Table-14 and figure-4). And therefore, formulation F3 with drug – polymer ratio 1:3 was found to be most promising formulation as it showed sustained release (89.57%) as well as maintained excellent matrix integrity during the period of 12 hr study. Hence formulation F3 was selected as the optimized formulation.

Table No. 14: % Release of Various Formulations

Sr. No.	Time (hr)	% Release ± S. D				
		L1	L2	L3	L4	L5
1	0	0	0	0	0	0
2	2	32.67±3.50	28.19±4.10	25.27±3.40	15.49±4.18	14.12±4.10
3	3	60.79±4.15	52.91±3.50	46.63±4.10	29.48±3.64	27.04±3.28
4	6	84.77±3.66	73.46±3.44	64.62±3.19	41.35±3.71	37.71±3.71
5	8		89.63±2.90	79.46±4.55	51.34±2.80	46.52±4.55
6	12			89.57±2.99	58.96±4.10	52.14±3.43

Each value represents the mean ± standard deviation

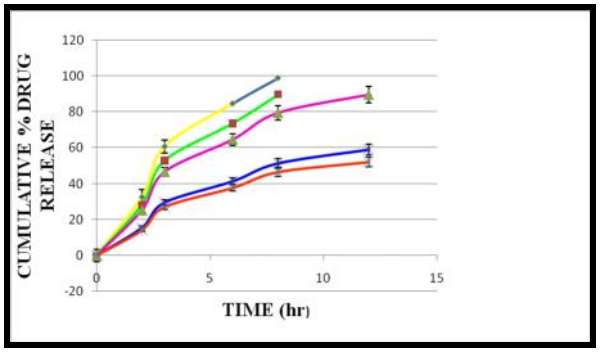

Fig. 4: Comparison of % Drug Release of Various Formulations

The optimized formulation (F_3) selected from the % drug release profiles was fitted into various kinetic models to know the mechanism of drug release from this formulation.The model that best fitted the release data was evaluated by regression coefficient (r^2). The best fit release kinetic model was found to be Higuchi for F3 formulation (Table-15 and figure-5,6,7 and8), which indicated release of the drug by diffusion from matrix type formulation. This means that specific narrow channels are produced in the matrix due to lactose erosion, through which the release of the drug takes place. Use of lactose as soluble filler (pore former), is preferable in designing inert matrices of sparingly soluble drugs. Drug release study indicated that nifedipine release was by diffusion from the insoluble matrix, which supported the study hypothesis that as a result of formation of a nifedipine molecular dispersion, nifedipine dissolution inside the matrix was no longer the rate-limiting step for drug release, and the drug diffusion in matrix through the channels formed by dissolution of lactose became the slowest step instead. The results of the present study indicate that the granules prepared using ethyl cellulose could be used for the sustained release of the drug.

Table No. 15: Fitting Data of the Release Rate Profile of F3 Formulation

Sr. No.	Release Models	R^2
1	Zero Order	0.836
2	First Order	0.702
3	Higuchi	0.971
4	Korsmeyer- Peppas	0.590

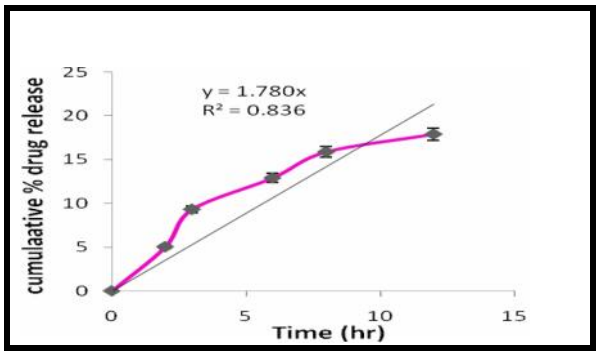

Fig. 5: Zero Order Plot of L3 Formulation

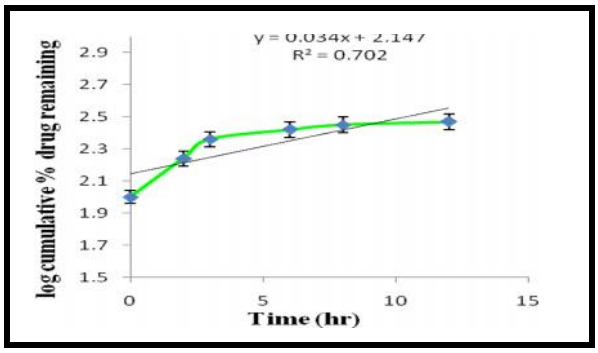

Fig. 6: First Order Plot of L3 Formulation

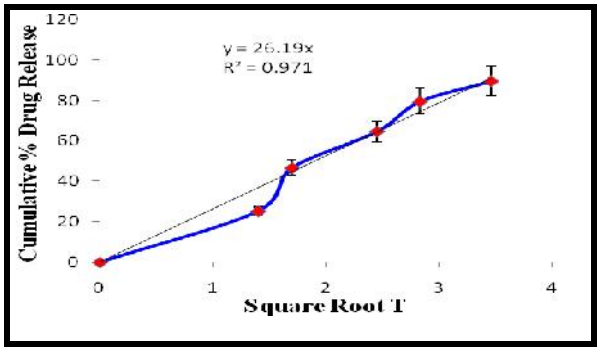

Fig. 7: Higuchi Plot of L3 Formulation

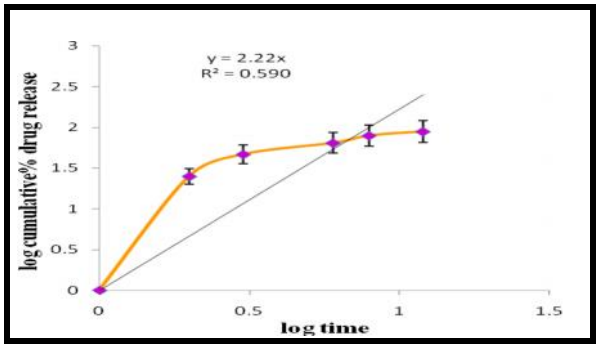

Fig. 8: Peppas Plot of L3 Formulation

CONCLUSION

The present work was aimed at exploitation of lactose as a pore former in designing inert matrix of poorly soluble drug (Nifedipine), further, at achieving sustained release for the period of 12 hours. The granules of Nifedipine were successfully prepared by wet granulation technique and confirmed that it is a good method for preparing Nifedipine loaded matrix granules for its higher percentage yield. Five different formulations of nifedipine matrix granules with varying amounts of lactose (65, 58.33, 51.66, 45 and 38.33%) were prepared successfully and were filled in size '2' hard gelatin capsules.

Capsules prepared by using these granulations exhibited desirable pharmacotechnical properties. Furthermore, the role of

filler solubility and its percolation has been shown to be important factors affecting the release behavior of the drug from inert matrices. Indeed, the results offered formulation researcher a cheaper option that incurs no additional cost that may arise if a material is to be replaced because of the need to improve on response parameters such as dissolution and drug release. In turn, it enabled to release the drug in sustained manner for prolonged time and thereby accompanying some of the benefits like reduction of total dose, frequency of administration, dose related side effects and better patient compliance. The results of the present study indicate that the granules prepared using ethyl cellulose could be used for the sustained release of the drug. Therefore, it was concluded that Lactosse can be successfully used to enhance drug solubility of poorly water soluble drugs like Nifedipine in sustained release inert matrices.

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