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Research

Formulation and evaluation of oral controlled release tablets Of nifedipine

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Abstract

The aim of the present study was to develop controlled release formulation of Nifedipine to maintain constant therapeutic levels of the drug for over 12 hrs. Karaya gum, Acacia and Tragacanth were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. From the dissolution studies it was evident that the formulation (F4) showed better and desired drug release pattern i.e., 98.14 % in 12 hours. It contains the Acacia polymer. It followed Zero order release kinetics mechanism.

Keywords: Nifedipine, Karaya gum, Acacia and Tragacanth, controlled release tablets.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.[1,2,3]

Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release

dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.[4,5]

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.[6]

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

A controlled release drug delivery system is capable of achieving the following benefits over conventional dosage forms:

- ✓ Total dose is low.
- ✓ Reduced GI side effects and other toxic effects.
- ✓ Reduced dosing frequency.
- ✓ Better patient acceptance and compliance.
- ✓ Less fluctuation in plasma drug levels.
- ✓ More uniform drug effect.
- ✓ Better stability of drug.[7,]

Advantages of Controlled Release Drug Delivery System

1] Therapeutic advantage: Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability: Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance: Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost: The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.

Avoid night time dosing: It also good for patients to avoid the at night time.[8,9,10]

Disadvantages

1] Dose dumping: Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] Less flexibility in accurate dose adjustment: In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

3] Poor In-vitro In-vivo correlation: In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.

4] Increased potential for first pass clearance: Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating anenzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.

5] Patient variation: The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patients.
6] Administration of controlled release medication does not permit prompt termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if significant adverse effects are noted, can not be accommodated.
7] There is danger of an ineffective action or even absence of it if the therapeutic substance is poorly absorbed from GIT.
8] Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make te product very difficult or sometimes impossible to prepare.
9] Therapeutical agents which absorbed by active transport are not good candidates for controlled release dosage form e. g. Riboflavin.
10] Economic factors must also be taken into account, since more costly processes and equipments are involved in manufacturing of many controlled release dosage forms.[11]

Factor Influencing the Formulation of Oral Controlled Release Drug Delivery System
Physicochemical Factors
Solubility

Low aqueous solubility drugs have low oral bioavailability. Drugs having good solubility in stomach are poor choice for controlled/sustained oral dosage forms. The water solubility limits the loading efficiency of drug into a variety of carrier systems such as liposome and micro particles, where highly water-soluble drug tend to leach fast from the carrier. The pH dependent solubility particularly in the physiological pH rangewould be another problem for controlled release formulation because of the variation in pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system allow to estimate contribution of three major factors Solubility, Dissolution and Intestinal Permeability which affect oral absorption. Class III (High solubility-Low permeability) and Class IV (Low solubility-Low permeability) drugs is poor candidate for controlled release dosage form.

Drug Stability

A drug in a solid state undergoes degradation at a much slower rate than a drug in suspension or solution[6],. Drugs that are unstable in gastric pH can be developed as slow release dosage form and the drugs can be delayed till the dosage form reaches the intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for oral controlled drug delivery systems.

Molecular Size and Diffusivity

Diffusivity defined as the ability of a drug to diffuse through membrane, is inversely related to molecular size. Diffusivity depends on size and shape of the cavities of the membrane. More than 95% of drugs are absorbed by passive diffusion. The upper limit of drug molecular size for passive diffusion is 600 Dalton. The examples of the drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

Partition coefficients

Partition coefficient id defined as the fraction of drug in an oil phase to that of an aqueous phase. It governs the permeation of drug particles through biological membrane. Drugs with high partition coefficient value easily permeate through biological membrane. The diffusion of drug molecules across rate controlling membrane or through the matrix system essentially relies on partition coefficient. Drugs that have lower partition coefficient are not suitable for oral controlled release drug delivery system and drugs that have higher partition coefficient are also not suitable for oral controlled drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

Drug pKa and ionization at physiological pH

Drugs existing largely in ionized form are poor candidate for oral controlled release drug delivery system because absorption rate of ionized drug is 3-4 times less than that of unionized form. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption.

MATERIALS AND METHODS

Nifedipine-Procured From Sun Pharma Ltd., India. Provided by SURA LABS, Dilsukhnagar and Hyderabad,Karaya gum-Research Lab Fine Chem Industries, Mumbai, Acacia-Research Lab Fine Chem

Industries, Mumbai, Tragacanth-Research Lab Fine Chem Industries, Mumbai, MCC-Shakti Chemicals, Mehsana, India, PVP K30-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium stearate-S. D. Fine Chemicals Ltd., Mumbai, India, Talc-S. D. Fine Chemicals Ltd., Mumbai, India

METHODOLOGY

Analytical method development

a) Determination of absorption maxima

100mg of Nifedipine pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

b) Preparation calibration curve

100mg of Nifedipine pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Nifedipine per ml of solution. The absorbance of the above dilutions was measured at 335 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the

sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 9.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Nifedipine. Total weight of the tablet was considered as 150 mg.

Procedure

1) Nifedipine and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 3: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nifedipine	10	10	10	10	10	10	10	10	10
Karaya gum	10	20	30	-	-	-	-	-	-
Acacia	-	-	-	10	20	30	-	-	-
Tragacanth	-	-	-	-	-	-	10	20	30
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Total weight	150	150	150	150	150	150	150	150	150

All the quantities were in mg, Total Tablet Weight = 150 mg

RESULT AND DISCUSSION

The present study was aimed to developing Controlled release tablets of Nifedipine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Nifedipine were taken in Simulated Gastric fluid (pH 1.2) and in pH 6.8 phosphate buffer at 335 nm and 338 nm respectively.

Table 4: Observations for graph of Nifedipine in 0.1N HCl (335 nm)

Concentration [µg/mL]	Absorbance
0	0
5	0.128
10	0.234
15	0.362
20	0.475
25	0.592

It was found that the estimation of Nifedipine by UV spectrophotometric method at λ_{max} 338 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was y = 0.023x+0.003.

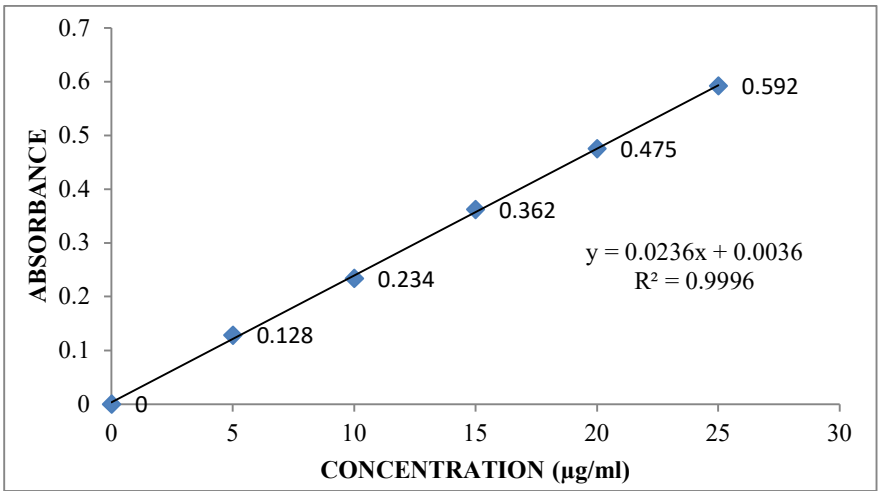

Fig 1: Standard graph of Nifedipine in 0.1N HCl

Table 5: Observations for graph of Nifedipine in p H 6.8 phosphate buffer (338nm)

Conc. [µg/ml]	Abs
0	0
5	0.155
10	0.272
15	0.423
20	0.562
25	0.676

It was found that the estimation of Nifedipine by UV spectrophotometric method at λ_{max} 338 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was y = 0.027x + 0.008.

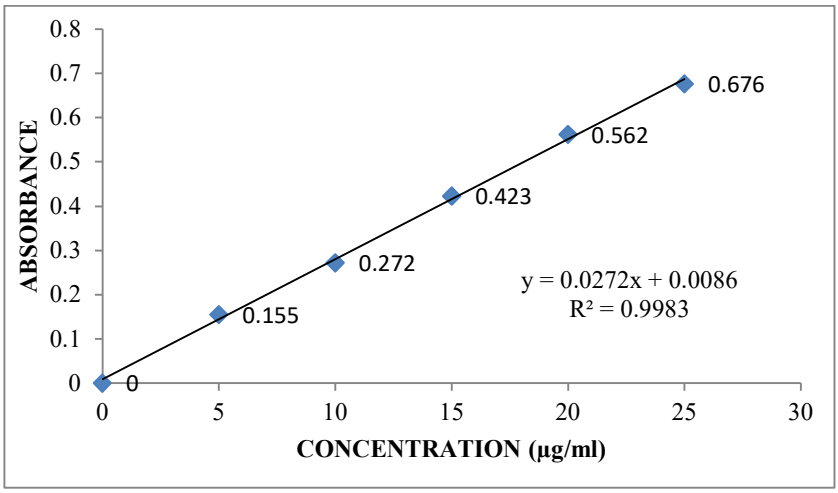

Fig 2: Standard graph of Nifedipine pH 6.8 phosphate buffer (338nm)

Preformulation parameters of powder blend

Table 6: Pre-formulation parameters of Core blend

Formulations	Bulk Density (gm/cm²)	Tap Density (gm/cm²)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Θ)
F_1	0.45	0.55	18.1	1.22	26.2
F_2	0.47	0.55	14.5	1.17	25.4
F_3	0.50	0.58	13.7	1.16	26.8
F_4	0.46	0.55	16.3	1.19	24.8
F_5	0.50	0.58	13.7	1.16	24.3
F_6	0.47	0.55	14.5	1.17	26.3
F_7	0.50	0.58	13.7	1.16	26.4
F_8	0.41	0.50	18.6	1.21	24.3
F_9	0.41	0.50	18.8	1.21	28.4

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41 to 0.50 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50 to 0.58 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 13.7 to 18.8 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.16 to 1.22 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 7: *In vitro* quality control parameters for tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm²)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	149.25	5.4	0.62	3.58	97.12
F2	147.10	5.9	0.48	3.25	99.81
F3	148.37	4.8	0.32	3.47	97.36
F4	149.65	5.7	0.49	3.16	99.32
F5	145.82	4.3	0.61	3.82	98.57
F6	150.2	5.8	0.25	3.65	96.87
F7	148.79	4.5	0.37	3.73	99.20

F8	149.28	4.6	0.18	3.19	97.56
F9	149.57	5.2	0.46	3.22	99.60

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 8: Dissolution Data of Nifedipine Tablets Prepared With Karaya gum Different Concentrations

Time	Cumulative Percent Drug Dissolved								
(Hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
0.5	6.15	9.10	14.98	15.82	11.98	10.54	8.24	11.73	7.06
1	9.62	14.53	18.60	21.57	15.63	15.96	17.56	16.90	18.29
2	16.98	18.86	23.54	27.49	20.75	19.48	25.43	28.53	22.02
3	20.83	27.54	29.72	32.26	27.14	26.41	32.29	32.16	28.96
4	26.47	35.99	35.34	40.52	33.60	33.24	42.59	42.24	36.10
5	29.68	39.42	40.75	46.14	37.59	38.67	47.63	55.97	41.57
6	35.89	44.27	46.18	57.38	40.37	43.68	50.15	61.24	47.98
7	38.50	49.38	52.26	68.89	45.10	52.11	58.66	68.85	52.31
8	46.76	54.18	58.74	74.14	58.81	56.93	62.34	72.31	58.92
9	49.10	58.92	61.36	83.63	66.95	61.40	73.59	76.21	66.22
10	57.17	63.34	65.82	87.75	68.31	67.29	76.91	84.78	78.19
11	62.32	67.15	76.96	93.50	77.18	72.57	79.87	87.62	86.98
12	66.80	73.43	86.51	98.14	90.67	85.23	86.14	96.54	90.23

From the dissolution data it was evident that the formulations prepared with Karaya gum polymer (high concentrations) were able to retard the drug release up to desired time period i.e., 12 hours. The Formulation Containing Acacia in 10 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.14 %. Whereas the formulations prepared with Tragacanth were retarded the drug release in the concentration of 20 mg (F8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.54 % in 12 hours with good retardation. From the above results it was evident that the formulation F4 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 9: Release kinetics data for optimised formulation

Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
15.82	**0.5**	0.707	1.199	-0.301	1.925	31.640	0.0632	-0.801	84.18	4.642	4.383	0.259
21.57	**1**	1.000	1.334	0.000	1.894	21.570	0.0464	-0.666	78.43	4.642	4.280	0.361
27.49	**2**	1.414	1.439	0.301	1.860	13.745	0.0364	-0.561	72.51	4.642	4.170	0.472
32.26	**3**	1.732	1.509	0.477	1.831	10.753	0.0310	-0.491	67.74	4.642	4.076	0.565
40.52	**4**	2.000	1.608	0.602	1.774	10.130	0.0247	-0.392	59.48	4.642	3.904	0.738
46.14	**5**	2.236	1.664	0.699	1.731	9.228	0.0217	-0.336	53.86	4.642	3.776	0.865
57.38	**6**	2.449	1.759	0.778	1.630	9.563	0.0174	-0.241	42.62	4.642	3.493	1.149
68.89	**7**	2.646	1.838	0.845	1.493	9.841	0.0145	-0.162	31.11	4.642	3.145	1.496
74.14	**8**	2.828	1.870	0.903	1.413	9.268	0.0135	-0.130	25.86	4.642	2.957	1.684

83.63	**9**	3.000	1.922	0.954	1.214	9.292	0.0120	-0.078	16.37	4.642	2.539	2.102
87.75	**10**	3.162	1.943	1.000	1.088	8.775	0.0114	-0.057	12.25	4.642	2.305	2.336
93.5	**11**	3.317	1.971	1.041	0.813	8.500	0.0107	-0.029	6.5	4.642	1.866	2.775
98.14	**12**	3.464	1.992	1.079	0.270	8.178	0.0102	-0.008	1.86	4.642	1.230	3.412

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy

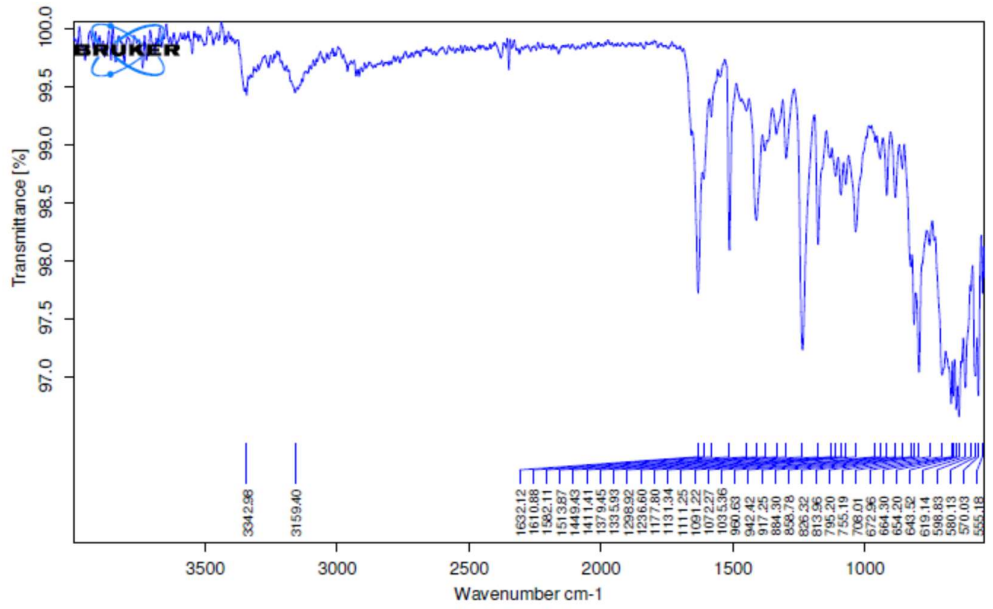

Fig 3: FT-IR Spectrum of Nifedipine pure drug

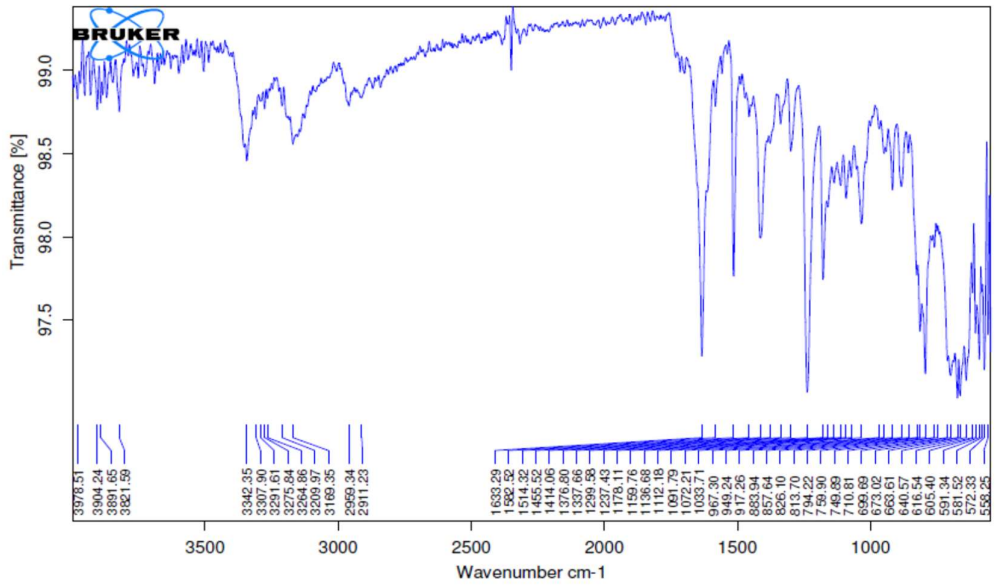

Fig 4: FT-IR Spectrum of Optimised Formulation

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

CONCLUSION

The present investigation was carried out for controlling the drug release up to 12 hrs. For controlling the drug release polymers used such as Karaya gum, Acacia and Tragacanth. From the investigation studies were found following: Standard graph was given that regression analysis R^2 value was 0.999 in 0.1 N HCl and 0.998 in pH 6.8 phosphate buffer. FTIR results were shown good compatibility between drug and excipients. All the pre and post compression studies such as Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio, Weight variation, Thickness, Hardness, Drug content were found to be within limits. *In vitro* drug release studies revealed that among all formulations F4 formulation was considered as optimised formulation which contains Acacia as polymer in the concentration of 10 mg. Drug release kinetic studies were done for optimised formulation. It was followed Zero order release kinetics.

Future scope

In vivo pharmacokinetic study will be prove that the Nifedipine from test tablets showed prolonged release and may be able to sustain the therapeutic effect. This can be further proved by pharmacodynamic study.

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