# FORMULATION AND INVITRO EVALUATION OF NICARDIPINE HYDROGEL BEADS

**Mekala Alekhya* G. Archana**

Department of pharmaceutics, Srikrishna devaraya University College of Pharmaceutical Sciences

Mekalaalekhya1530@gmail.com archana.pharma156@gmail.com

**Abstract:**

The aim of the present work is to provide a therapeutic amount of Nicardipine to the proper site in the body and also to achieve and maintain the desired concentration. Nicardipine is slightly soluble in water. It is having 8.6 hour half life and low bioavilability. In the present study eleven formulations were formulated by using sodium alginate,xantha gum, guar gum and karaya gum different proportions by using ionotropic gelation method. The FTIR Spectra revealed that, there was no interaction between polymers and Nicardipine. As the polymer ratio was increased, the mean particle size of Nicardipine hydrogel beads was also increased. From the results it can be inferred that there was a proper distribution of Nicardipine in the hydrogel beads and the deviation was within the acceptable limits. On the basis of release data and graphical analysis formulation **F9** containing karaya gum and guar gum in 1:1.5:2 ratio showed a good controlled release profile up to 12 hrs with maximum entrapment efficiency because of high polymer concentration and follows zero order kinetics with super case II transport mechanism.

**Keywords**: Nicardipine, FTIR,SEM, sodium alginate, Guar gum, Xanthan gum, Karaya gum.

# 1. INTRODUCTION

The oral administration of pharmaceutical dosage forms is the more usual, convenient and comfortable route for active drug delivery to the body. Oral controlled release systems continue to be the most popular ones among all the drug delivery systems as it offers several advantages over the conventional systems like:

- Improve patient's compliance and convenience due to less frequent dosing of drug.
- Reduction in fluctuation of steady state plasma level and therefore helps in better control of disease condition.
- Maximum utilization of drug enabling reduction in total amount of dose administered.  Reduction in health care cost through improved therapy, shorter treatment period and less frequency of dosing [1,2].

There are various approaches in delivering a therapeutic substance to the target site in a controlled release fashion. One such approach is using microspheres as carriers for drugs. However, these formulations have to be injected either subcutaneously or intravenously, which in general is not acceptable. Hence, there is a need to develop an oral drug delivery system that is convenient for patients. Various natural polymers like Chitosan, Gelatin and Na CMC have been used to develop drug delivery systems for entrapping and delivering drugs orally[3].

## 1.1 CONTROLLED DRUG DELIVERY

One of essential issues of drug formulation is the controlled release of drugs, which can improve therapeutic efficacy by offering prolonged in vivo action, controlled blood concentration as well as tissue-targeted local release [3-4]. A possible approach to the controlled and sustained release of drugs involves incorporation of drug molecules into the biodegradable polymer microspheres.

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant or cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. The release patterns of drug from both formulations traditional and controlled are given in fig

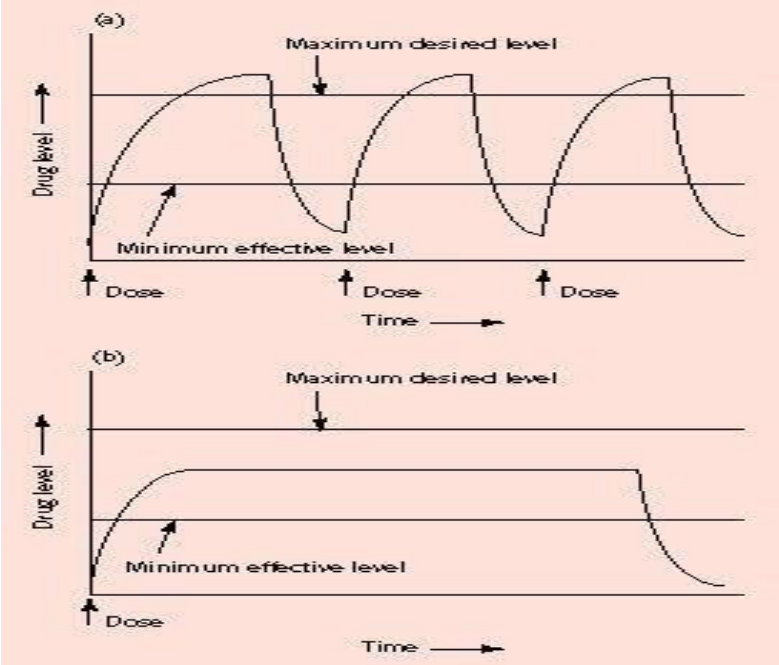



**Fig: Drug levels in the blood with (a) traditional drug dosing and (b) controlled-delivery dosing**

Controlled release refers to the use of a delivery device with the objective of releasing the drug into the patient body at a predetermined rate, or at specific rimes or with specific release profiles. This could revolutionize the manner of medication and offer following advantages along with some disadvantages.

Table Advantages and disadvantages of control release dosage forms

| **Advantages** | **Disadvantages** |
|---|---|
| Reduction in dosing frequency | High cost |
| Reduced fluctuations in circulatory drug levels | Unpredictable or poor in vitro – in vivo correlation |
| Avoidance of night patient compliance | Dose dumping |
| Increased patient compliance | Reduced potential for dosage adjustment |
| Mire uniform effect | Increased first pass clearance |
| Decreased side effects like reduced GI irritation | Poor systemic availability in general |

Various characteristics of drug molecule that render it unsuitable for controlled release dosing

- Narrow therapeutic index

- Short/long elimination half life
- Poor absorption
- Active absorption large doses
- Low aqueous solubility
- Extensive first pass metabolism
- Incompatible pharmacological effects and
- Circulation time course
- Controlled-Release mechanisms

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale through pores in the polymer matrix or on a molecular level, by passing between polymer chains.

Biopharmaceutical aspects of regulatory requirement and new drug applications The controlled release formulation developed should aim to accomplish two important Objectives:

- It should allow a maximum possible percentage of the dose in the formulation to be absorbed in controlled manner.
- It should be capable of minimizing patient-to-patient variability.

Over the past three decades, considerable research interest has arisen worldwide in the development of new colloidal drug delivery systems. The ideal colloidal delivery system could transport the associated drug to its desired site of action and then release it at an optimum rate. The carrier itself should be non-toxic and able to be degraded in vivo so that it does not accumulate indefinitely in the tissues. The colloidal preparation also needs to be pharmaceutically acceptable with regards to stability and ease of administration. Microencapsulation is a technology devoted to entrapping solids, liquids, or gases inside one or more polymeric coatings.

Microencapsulation helps to separate a core material from its environment until it is released. It protects the unstable core from its environment, thereby improving its stability, extends the core’s shelf life and provides a sustained and controlled release.

## 1.2 MICROSPHERES

There are various approaches in delivering a therapeutic substance to the target site in a controlled release fashion. One such approach is using microspheres as carriers for drugs.

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations. Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa4 .

**Materials Used:**

Microspheres used usually are polymers.

They are classified into two types.

1. Synthetic Polymers
2. Natural polymers

Synthetic polymers are divided into two types.

**i. Non-biodegradable polymers**

- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate  Epoxy polymers **ii. Biodegradable polymers [5,6]**
- Lactides, Glycolides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.[7, 8]

**A] Proteins: [9-10]**

- Albumin
- Gelatin
- Collagen

**B] Carbohydrates:**

- Agarose
- Carrageenan
- Chitosan
- Starch

**C] Chemically modified carbohydrates: [11]**

- Poly dextran
- Poly starch.

**TYPES OF MICROSPHERE [12-22]**

1. **Bioadhesive Microspheres**

   Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

2. **Magnetic Microspheres**

   This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres. i. Therapeutic Magnetic Microspheres: It is used to deliver chemotherapeutic agent to liver tumor.

   Drugs like proteins and peptides can also be targeted through this system. ii. Diagnostic Microspheres: It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

3. **Floating microspheres**

   In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

4. **Polymeric Microspheres**

   The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

   **i. Biodegradable Polymeric Microspheres:**

   Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is

in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. **ii. Synthetic Polymeric Microspheres:**

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

## ADVANTAGES

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology all owes a controllable variability in degradation and drug release.

## LIMITATIONS[23]

Some of the disadvantages were found to be as follows:

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed.

## CHARACTERISTICS OF MICROSPHERES:

Table: Microsphere property

| S.No: | Property | Consideration |
|---|---|---|
| **1** | Size Diameter | Uniformity/distribution |
| **2** | Composition | Density,RefractiveIndex,Hydrophobicity/hydrophilicity Nonspecific binding Autofluorescence |
| **3** | Surface Chemistry | Reactive groups Level of functionalization Charge |
| **4** | Special Properties | Visible dye/fluorophore Superparamagnetic |

1. Microsphere size may be critical to the proper function of an assay, or it may be secondary to other characteristics. Considering traditional diagnostic methods, the test or assay format commonly dictates particle size, such as the use of very small spheres (~0.1- 0.4μm) to ensure satisfactory wicking in lateral flow tests, or the use of larger, cell-sized spheres (~4-10μm) for bead based flow cytometric assays.

2. Common microsphere compositions include polystyrene (PS), poly(methyl methacrylate) (PMMA), and silica. These materials possess different physical and optical properties, which may present advantages or limitations for different applications. Polymer beads are generally hydrophobic, and as such, have high protein binding abilities. However, they often require the use of some surfactant (e.g. 0.01-0.1% Tween® 20 or SDS) in the storage buffer to ensure ease of handling. During synthesis, functional monomers may be co-polymerized with styrene or methyl methacrylate to develop beads with surface reactive groups. Functional groups may be used in covalent binding reactions, and also aid in stabilizing the suspension. Silica microspheres are inherently hydrophilic and negatively charged. Consequently, aqueous silica suspensions rarely require use of surfactants or other stabilizers. Carboxyl- and amine functionalized silica spheres are available for use in common covalent coating protocols, and plain silica microspheres may be modified using a variety of silanes to generate functional groups or alter surface properties.

3. Microspheres may be coated with capture molecules, such as antibodies, oligonucleotides, peptides, etc. for use in diagnostic or separation applications. Microsphere coatings are typically optimized to achieve desired specific activity, while minimizing nonspecific interactions. Consideration should also be given to the required stability, development time frame and budget, and the specific biomolecule to be coated. These factors will aid in determining the most fitting coating strategy for both short- and long-term objectives. Standard microsphere products support three basic coating strategies: adsorption, covalent coupling, and affinity binding.

4. Many applications in the life sciences demand added properties, such as fluorescence or a visible color, or iron oxide inclusions for magnetic separations. Polymer spheres (and polymer based magnetic spheres) are often internally dyed via organic solvent swelling, and many standard products are available. Dye concentrations can be adjusted to produce beads with different intensities to meet special needs, such as QuantumPlex™ for multiplexed flow cytometric assays, or our Dragon Green or Flash Red Intensity Standards, which support imaging applications and associated instrument QC. Many surface- or internally labelled fluorescent beads are also available as specialized flow cytometry standards[24].

**CRITERIA FOR MICROSPHERE PREPARATION:**

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique[25]. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, coprecipitation etc[26].

Preparation of microspheres should satisfy certain criteria[27]:

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

**METHOD OF PREPERATION:**

The various methods of preparations are:

**Emulsion Solvent Evaporation Technique:**

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs[28].

**Emulsion Cross Linking Method:**

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40 0C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 oC, results in w/o emulsion then further stirring is done for 10 min at 150 C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 370 C for 10 min to block unreacted glutaraldehyde.18 Examples for this technique is Gelatin A microspheres.

**Coacervation Method:**

Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 800 C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twicely with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

Coacervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin 5 times with continuous stirring.1After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50o C for 4 hr.

**Spray Drying Technique:**

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent29. Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may loose crystalinity due to fast drying process[29].

**Emulsion-Solvent Diffusion Technique:**

In order to improve the residence time in colon floating microperticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added dropwise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following microparticles were sieved and collected[29].

**Multiple Emulsion Method:**

Oral controlled release drug delivery of various drugs was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The the primary emulsion was then reemulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase[29].

**Ionic Gelation Method:**

Alginate/chitosan particulate system for was prepared using this technique.Different % (w/v) of drug was added to 2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 6 hrs & 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 7.4 but the drug did not release in acidic pH29,[30].

**Quassi Emulsion Solvent Diffusion[31]:**

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40ºC for a day.

**Physicochemical Evaluation:**

**Characterization[32]**

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

**Particle Size and Shape[33]**

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy1 is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres.

**Electron Spectroscopy for Chemical Analysis:**

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

**Attenuated total reflectance Fourier TransfomInfrared Spectroscopy:**

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

**Density Determination:**

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

**Isoelectric Point:**

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The mean velocity at different Ph values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

**In - Vitro methods [34]**

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.

**Beaker Method [35, 36, 37, 38]:**

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.

**Interface Diffusion System**

This method is developed by Dearden & Tomlinson. It consists of four compartments. The compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.

**Modified Keshary Chien Cell [39, 40]:**

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.

**Dissolution Apparatus: [41-49]**

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle and basket. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.

**Other Methods:**

Few other methods involving plexi glass sample blocks placed in flasks, agar gel method, ValiaChein cell USP n2 III dissolution apparatus,etc have also been reported. Although a number of methods have been reported, the ideal method would be one where sink condition is maintained and dissolution time in vitro simulates dissolution time in vivo.

## 2. AIM AND OBJECTIVE

Nicardipine is a calcium channel blocker used for the short-term treatment of hypertension and chronic stable angina. The terminal elimination half life is about 8.6-14.4 hrs. So to enhance the bioavailability of Nicardipine, controlled release hydrogel beads were formulated by using ionotropic gelation method. The relatively high water content of hydrogels makes them also permeable to small molecules like oxygen, nutrients, and metabolites. This high solute permeability makes them ideal materials of choice as devices for the controlled release of many drugs and other active agents.

**In this present investigation it was proposed.**

- To formulate Nicardipine hydrogel beads using polymers sodium alginate, Guar gum, Xanthan gum, and Karaya gum for controlled drug delivery, and also to compare the release kinetics of Nicardipine beads.
- To evaluate the polymer characteristics and Nicardipine gel beads characteristics.
- To evaluate physico-chemical characteristics like drug interaction study (FTIR), surface morphology (SEM)etc.
- To evaluate the drug Content estimation of the formulations.
- To perform *in vitro* dissolution studies.
- To evaluate the release kinetics.

## 3.PLANOFWORK

### ❖Preformulationstudies

- Solubility
- Spectrophotometric studies
- Drug-interaction study(FTIR)

### ❖Formulation of Beads

Preparation of Nicardipine hydrogel beads using polymers viz. sodium alginate, guar gum, Xanthan gum, Karaya gum for Controlled drug delivery by using ionotropic gelation method.

❖**Evaluationstudies**

- Surface morphology (SEM)
- Particle size distribution of prepared Nicardipine hydrogel beads
- Drugentrapment efficiency
- *In vitro* dissolution studies
- Kinetics of drug release

## 4. REVIEW OF LITERATURE

**S Takka et al et al,[50]** The release rate of nicardipine HCl from various alginate gel bead formulations was investigated. The formulations were prepared by utilizing 23 factorial design. The effect of drug:polymer weight ratio, CaCl2 and sodium-alginate concentration on the time for 50% of the drug to be released (t50%) and the drug entrapment efficiency were evaluated with analysis of variance. The mean particle size and the swelling ratio of the beads were determined. The in vitro release studies were carried out by flow-through cell apparatus in different media (pH 1.2, 2.5, 4.5, 7 and 7.5 buffer solutions). Drug:polymer weight ratio and the interaction of drug:polymer weight ratio and CaCl2 concentration had a significant effect on the drug entrapment efficiency. The release of nicardipine was extended with the alginate gel beads, which were prepared in a ratio of 1:1 (drug:polymer). The release of drug from alginate gel beads took place both by diffusion through the swollen matrix and relaxation of the polymer at pH 1.2-4.5. However, the release was due to the diffusion and erosion mechanism at pH 7-7.5.

**Ya-Ni Dai etal,[51]** A novel N-succinyl chitosan(Suc-Chi)/alginate hydrogel bead was prepared by the ionic gelation method for the controlled delivery of nifedipine. The structure and surface morphology of the hydrogel were characterized by FTIR and SEM, respectively. Factors influencing the swelling ability of the hydrogel bead were also investigated, such as the ratio of Suc-Chi and alginate (X1), the weight ratio of drug to polymer (X2), the volume ratio of alginate/Suc-Chi to CaCl2 (X3), crosslinking time (X4), CaCl2 concentration (X5). In addition, the delivery behavior of nifedipine from the hydrogel bead was studied. The amount of nifedipine released from the hydrogel bead at pH 1.5 was relatively low (11.6%), while this value approached 76% at pH 7.4. The results clearly suggested that the Suc-Chi/alginate hydrogel bead may be a potential polymeric carrier for drug delivery in the intestinal tract. The release of nifedipine from the hydrogel bead at various pH values was analysed by a semiempirical equation and it was found that the drug release mechanisms were either ‘anomalous transport’ or ‘case-II transport’. Copyright © 2008 John Wiley & Sons, Ltd.

**Xu-Jiang Zhu etal,[52]** A novel N-succinyl chitosan/alginate hydrogel bead was prepared by the ionic gelation method for controlled delivery of nifedipine (NF). Objective: The delivery

behavior of NF from the hydrogel bead was studied in rabbit body. Materials and methods: Nitrendipine was used as the internal standard and the concentration of NF in serum was determined by reversed-phase high-performance liquid chromatography. Results: The assay was linear from 5 to 755 ng/mL. The limit of quantitation for NF was 5 ng/mL in serum, and the recovery was greater than 90%. The method was used to determine the concentration–time profiles of NF in the serum. The pharmacokinetic parameters were calculated by Drug and Statistics (ver 1.0) program. The mean Cmax was 320.2 ± 71.3 μg/L, the mean Tmax was 3.2 ± 0.5 hours, the mean t1/2 was 6.60 ± 2.17 hours, the mean AUC0-24 was 2.03 ± 0.25 mg h/L, the mean AUC0-∞ was 2.50 ± 0.36 mg h/L, the mean MRT0-24 was 8.57 ± 0.19 hours, and the mean MRT0-∞ was 15.2 ± 1.8 hours. Discussion and conclusion: The pharmacokinetic characteristics were found by a two-compartment model following the oral administration of NFloaded N-succinyl chitosan/alginate hydrogel beads in rabbits.

**Shivhare UD etal,**[53] The objective of present study was to formulate hydrogel beads for the sustained delivery of Nifedipine using different polymer ratio and to study the in-vitro release characteristics of hydrogel beads. The sodium alginate/chitosan crosslinked hydrogel beads of Nifedipine were prepared by the ionotropic gelation method. The hydrogel beads were showed very little drug release under pH 1.5 HCl buffer whereas the release was increased in simulated gastrointestinal fluid (pH 6.8 phosphate buffer). The drug release was found to be affected by the varying ratio of sodium alginate and chitosan as well as percentage of total polymer. The results of stability study indicated that there was no significant variation in the drug release profile of the optimize batch F12 and F13 during the three month study. Therefore, the prepared sodium alginate/chitosan hydrogel beads can be considered as potential candidate for sustained delivery of Nifedipine to the intestine. Hydrogel beads, Nifedipine, Sodium alginate, Chitosan.

**Ya-Ni Dai etal,**[54] he aim of the present work was to investigate the swelling behavior and in vitro release of nifedipine from alginate–chitosan hydrogel beads. Structure and surface morphology of the hydrogel were characterized by FTIR and SEM, respectively. Alginate–chitosan mixed beads and alginate–chitosan coated beads were prepared by ionic gelation method. The swelling ability of the beads and in vitro release of nifedipine in simulated gastric fluid (pH 1.5) and different phosphate buffer solutions (pH 2.5, 5.0, 6.8, 7.4, and 8.0) were found to be dependent on the presence of the polyelectrolyte complex between chitosan and alginate.

The amount of nifedipine released from the mixed beads at pH 1.5 was relatively low (42%), whereas this value approached to 99% at pH 6.8. In comparison with the mixed beads, the released nifedipine from the coated beads was minimal at pH 1.5 (18%), whereas ~99% nifedipine was released at pH 6.8. The results suggested that the coated beads can hold drug better at low pH than the mixed beads and show excellent pH sensitivity. Therefore, the alginate–chitosan coated beads could be a suitable polymeric carrier for drug delivery in the intestinal tract. © 2008 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2008

**Sevgi Takka etal,**[55]The release rate of nicardipine HCl from various alginate gel bead formulations was investigated. The formulations were prepared by utilizing 23 factorial design.

The effect of drug:polymer weight ratio, CaCl2 and sodium-alginate concentration on the time for 50% of the drug to be released (t50%) and the drug entrapment efficiency were evaluated with analysis of variance. The mean particle size and the swelling ratio of the beads were determined. The in vitro release studies were carried out by flow-through cell apparatus in different media (pH 1.2, 2.5, 4.5, 7 and 7.5 buffer solutions). Drug:polymer weight ratio and the interaction of drug:polymer weight ratio and CaCl2 concentration had a significant effect on the drug entrapment efficiency. The release of nicardipine was extended with the alginate gel beads, which were prepared in a ratio of 1:1 (drug:polymer). The release of drug from alginate gel beads took place both by diffusion through the swollen matrix and relaxation of the polymer at pH 1.2-4.5. However, the release was due to the diffusion and erosion mechanism at pH 7-7.5.

**Sanjay K. Jain.**[56] Chitosan hydrogel beads were prepared by the cross-linking method followed by enteric coating with Eudragit S100. All formulations were evaluated for particle size, encapsulation efficiency, swellability, and in vitro drug release. The size of the beads was found to range from 1.04 ± 0.82 mm to 1.95 ± 0.05 mm.The amount of the drug released after 24 hours from the formulation was found to be 97.67% ± 1.25% in the presence of extracellular enzymes as compared with 64.71% ±1.91% and 96.52% ± 1.81% release of drug after 3 and 6 days of enzyme induction, respectively, in the presenceof 4% cecal content. Degradation of the chitosan hydrogel beads in the presence of extracellular enzymes as compared with rat cecal and colonic enzymes indicates the potential of this multiparticulate system to serve as a carrier to deliver macromolecules specifically to the colon and can be offered as a substitute in vitro system for performing degradation studies. Studies demonstrated that orally administered chitosan hydrogel beads can be used effectively for the delivery of drug to the colon.

**K.M. Manjanna.et.al.**[57]**,** prepare and evaluate calcium alginate (CA) microbeads with calcium chloride as cross-linking agent for aceclofenac sodium by ionotropic external gelation method. Calcium alginate microbeads represent a useful tool for oral sustained/ controlled drug delivery but show several problems, mainly related to the stability, and rapid drug release at higher pH that, in most cases, is too fast due to increase porosity. To overcome such inconveniences, which was to develop CA microbeads coated with Guar gum (GG) and Locust bean gum (LBG) as drug release modifiers to improve stability and prolong the drug release. While increasing in the concentration of sodium alginate and other polymer dispersion increased size distribution, flow properties, mean particle size, swelling ratio and drug entrapment efficiency. The mean particle sizes of drug-loaded microbeads were found to be in the range 596.45±1.04 to 880.10±0.13. The drug entrapment efficiency was obtained in the range of 63.24±0.66 to 99.75±0.87. The shape and surface characteristics were determined by scanning electron microscopy (SEM). No significant drug-polymer interactions, physical changes and crystallinity of the drug in the formulations were determined by FT-IR spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction [XRD]. In-vitro drug release profiles of microbeads were pH dependent and were analyzed by different kinetic models. The mechanism of drug release from microbeads depends on swelling and erosion process resulting CA microbeads was diffusion controlled followed by First order kinetics and whereas CA microbeads coated with GG and LBG approaching to near Zero- order kinetics.

**Pitta. Lavanya.et.al.[58],** Formulate and evaluate modifiedrelease oral Hydrogel Beads of an anti diabetic drug**.** The hydrogel beads were synthesized by physical cross-linking polymerization technique using, N,N′-Methylene bis acryl amide as cross linker. The swelling studies showed a higher swelling in basic pH and a minimal swelling in acidic pH. From the swelling ratio it was found that the swelling of the hydrogel beads were pH depended and at PKa value (3-4) of acrylic acid the swelling showed a decreased value. From the diffusion study it was concluded that as the acrylic acid concentration increased and cross linker decreased the diffusion coefficient was increased. The *in- vitro* release data showed that, as the concentration of Cross-linking agent was increased; swelling decreased resulting in decreased release of the drug. From the results, it can be deduced that the acrylic acid-Sodium alginate hydrogel beads could be suitable as a controlled drug delivery system for the anti diabetic drug Gliclazide.

**BHATT M. B.et.al.[59],** formulate and evaluate the sustained release hydrogel beads of valsartan using different ratio of polymer and counter ion in order to increase the drug bioavailability, therapeutic efficiency, reduce dosing frequency and improvement of patient compliance. Different formulations were prepared by ionotropic gelation method using various release rate controlling polymer i.e. gellan gum and counter ion like,calcium chloride. Drug-excipients compatibility was carried out by FTIR. Different formulations were evaluated for particle size, swelling index, % drug entrapment efficiency and *in vitro* drug release. Optimized batch was evaluated for scanning electron microscopy. Mathematical analysis of the release kinetics was carried out to determine the mechanism of drug release. *Invitro* release data was fitted to various models to ascertain the kinetic of drug release. Response surface graph was prepared to examine the effect of independent variable on dependent variable. A 32 factorial was applied to check the effect of varying the concentration of gellan gum (X1) and calcium chloride (X2) on the dependent variable i.e. swelling index and *in vitro* drug release. It was observed that optimized batch A7 containing gellan gum (2.5%) and calcium chloride (4%) gives 123 % swelling index after 12 hrs and 100.56 % drug release after 24 hrs, which is nearer to theoretical profile.

**Payal Deepak.et.al.[60],** formulate pioglitazone loaded chitosan polyelectrolyte complex (PEC) hydrogel beads by ionotropic gelation technique using sodium tripolyphosphate (TPP) as an ionic cross linking agent. These PEC hydrogel systems are based upon the fact that their biodegradable polymeric network can capture the drug to release in a sustained manner. Different formulations of pioglitazone loaded microbeads were characterized for particle size, surface texture analysis, drug entrapment efficiency, *in vitro* drug release studies and kinetics and *in vitro* mucoadhesion test etc. The optimized formulation was found to be spherical with rough surface, free flowing and white in colour. The particle size range was found to be from 570±33.60µm to 705±34.44µm with entrapment efficiency in the range of 64.51±1.44% to 88.23±1.35%. The optimized formulation showed a better release profile of 84.39% among all the five formulations at the end of 12 h and follows Higuchi release kinetics. Thus, it can be concluded that the Pioglitazone loaded chitosan microbeads could be productively formulated by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.

**J. S. Patil et.al.,**[61] Prolonged release drug delivery system of stavudine was made by ionotropic gelation and polyelectrolyte complexation technique. Cross-linking reinforced chitosan-gellan complex beads were prepared by gelation of anionic gellan gum, the primary polymer, with oppositely charged counter ion to form beads which were further complexed with chitosan as a polyelectrolyte. The effect of this polymer on release profile of drug was studied. Beads without chitosan complexation were also made. The reaction of chitosan-gellan complex dominates the formation of skin layer on the surface of beads. Stavudine an antiretroviral drug was selected as novel drug for the experiment. The final formulations were subjected to *in vitro* evaluation and several characterization studies. Batches with gellan gum shows Higuchi model, while chitosangellan shows zero order release. All the batches with copolymer showed sustained the drug release more than 12 h, whereas with gellan gum alone showed up to 10 h. Batches with chitosan showed maximum drug encapsulation efficiency.

**Maiti, Sabyasachi et.al.,**[62] locust bean gum (LBG) was chemically modified to its carboxymethyl sulfate derivative (CSLBG) and characterized by its degree of sulfation and carboxymethylation. Ionotropic gelation of aqueous CSLBG droplets led to the formation of hydrogel beads (17771879 µm) in presence of basic aluminum chloride solution. A potent analgesic tramadol hydrochloride (BCS class I) was incorporated into the hydrogel beads in various amounts (20, 30 and 40%, w/w). Irrespective of initial drug loading, the beads were spherical under scanning electron microscope but distortion was noted after drying. The beads were capable of entrapping a maximum of 53.28% drug. The hydrogels disintegrated in 3-5min and liberated almost all of their content in 15min in 0.1(N) HCl solution. A statistically significant difference was noted in $t_{85\%}$ values of the formulations ($p < 0.05$). FTIR spectroscopy did not reveal any chemical interaction between drug and CSLBG. Differential scanning calorimetry and X-Ray diffraction analyses suggested amorphous dispersion of the drug after its encapsulation into the hydrogel beads. CSLBG hydrogel beads satisfied the single point dissolution test criteria as set by US FDA (NLT 85% in 15min) for immediate release dosage forms and thus, could be useful in achieving immediate analgesic action of the drug.

**Qing Sheng Zhao et.al.,**[63] Chitosan hydrogel beads were successfully prepared by the method of thermosensitive internal gelation technique. The prepared beads were spherical, smooth-surfaced and non-aggregated with a diameter of 1.7–2.1mm. The diameters of beads can be controlled and have a correlation with the initial drop size, the concentration of CaCl2, alginate and the time of solidification. The bead is comprised of three parts, which are chitosan/glycerophosphate (CS/GP) hydrogel core, chitosan-alginate (CS/SA) gel layer in the middle and calcium-alginate gelatin capsules in outer layer. Swelling studies indicate that the beads can be stable in simulated gastric fluid. But the beads shrink sharply when removed to simulated intestinal fluid. Drug release behavior showed that release of ornidazole in the beads is much slower than in the CS/GP hydrogel.

# 5.DRUG &EXCIPIENTS PROFILE

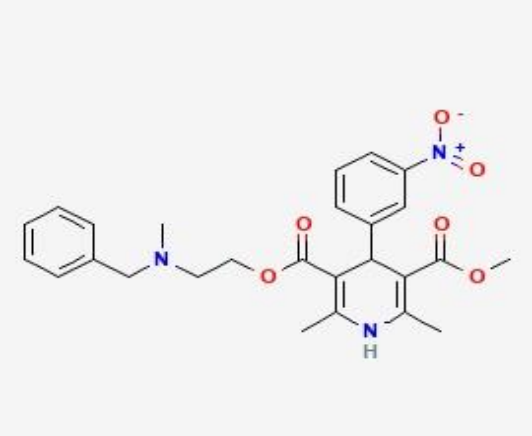
## 5.1. Drug Profile[69]

### 5.1.1. Nicardipine.

**Description:**

Nicardipine is a calcium channel blocker used for the short-term treatment of hypertension and chronic stable angina.

**Structure:**



**Structure of Nicardipine**

**Synonyms:**

Nicardipine
Nicardipino
Nicardipinum

**CAS number**

55985-32-5

**Weight**

**Average:** 479.525gm/mol.
**Monoisotopic:** 479.205635675

**Chemical Formula:**

C26H29N3O6

**IUPAC Name:**

3-{2-[benzyl(methyl)amino]ethyl}5-methyl2,6-dimethyl-4-(3-nitrophenyl)-1,4dihydropyridine-3,5-dicarboxylate

**PHARMACOLOGY:**

**Indication:**

Used for the management of patients with chronic stable angina and for the treatment of hypertension.

**Pharmacodynamics:**

Nicardipine, a dihydropyridine calcium-channel blocker, is used alone or with an angiotensinconverting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Nicardipine is similar to other peripheral vasodilators. Nicardipine inhibits the influx of extra cellular calcium across the myocardial and vascular

smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

**Mechanism of action:**

By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, nicardipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

**Absorption:**

While nicardipine is completely absorbed, it is subject to saturable first pass metabolism and the systemic bioavailability is about 35% following a 30 mg oral dose at steady state.

**Volume of distribution:**

8.3 L/kg

**Protein binding:**

>95%

**Metabolism:**

Nicardipine HCl is metabolized extensively by the liver.

**Route of elimination:**

Nicardipine has been shown to be rapidly and extensively metabolized by the liver.

**Half life :** 8.6 hours

**Drug Interactions:**

**1,2-Benzodiazepine:**1,2-Benzodiazepine may increase the central nervous system depressant (CNS depressant) activities of Nicardipine.

**Abametapir**:The serum concentration of Nicardipine can be increased when it is combined with Abametapir.

**Abatacept:**The metabolism of Nicardipine can be increased when combined with Abatacept.

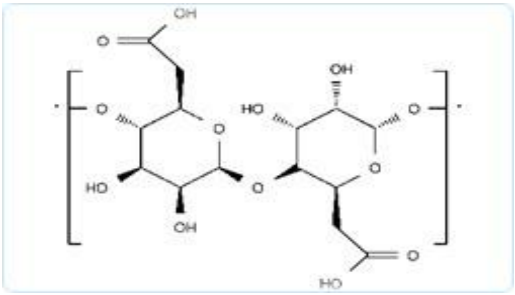
**Adverse effect:**

- Headache.
- Upset Stomach.
- Dizziness or Lightheadedness.
- Excessive Tiredness.
- Flushing.
- Numbness.
- Fast Heartbeat.
- Muscle Cramps.

## 5.2. POLYMERPROFILES[70]

### 5.2.1. SODIUM ALGINATE:

**Chemical structure;**



**Nonproprietary Names:**
BP: Sodium Alginate
PhEur: Sodium Alginate USP-NF: SodiumAlginate
**Synonyms :**
Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol;Keltone;natriialginas; Protanal; sodium polymannuronate.
**Chemical Name and CAS Registry Number:**

Sodiumalginate[9005-38-3]

**Empirical Formula:**

(C6H7O6Na)n
**Functional Category:**
Stabilizing agent; Suspending agent; Tablet and capsule disintegrant; Tablet binder; Viscosity increasing agent.of sodium chlorideis present.

**Applications in Pharmaceutical Formulation:**

- Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. ➢ In tablet formulations,sodiumalginate may be used as both a binder and disintegrant;
- It has been used as a diluent in capsule formulations

- Sodiumalginatehas alsobeen used in thepreparation of sustainedrelease oral formulationssinceitcan delaythedissolution of adrugfromtablets.
- Aqueous suspensions.

- Theeffectsofparticlesize,viscosity andchemicalcompositionofsodiumalginateon drug release from matrix tablets havebeendescribed.

**5.2.2. Guar Gum :**

**Nonproprietary names:**

BP: Guar galactomannan

PhEur: Guar galactomannanum

USPNF: Guar gum.

**Regulatory status**

GRAS listed. Accepted as a food additive in Europe. Included in the FDA. Inactive ingredients guide (oral suspensions, syrups, and tablets; topical preparation, vaginal tablets). Included in nonparental medicines licensed in UK.

**Synonyms**

E412; Galactosol; guar flour; jaguar gum; Meyprogat; Meyprodor; Meyprofin.

**Chemical name and CAS number**

Galactomannan polysaccharide [9000-30-0]

**Molecular formula:**

$(C_6H_{12}O_6)_n$ _220 000

**Structure formula:**

Guar gum consists of linear chains of (1!4)-b-D-mannopyranosyl units with a Dgalactopyranosyl units attached by (1!6) linkages. The ratio of D-galactose to D- mannose is between 1 : 1.4 and 1 : 2

**Description:** Guar gum occurs as an odorless or nearly odorless, white to yellowish- white powder with a bland taste.

**Typical Properties**

a) Sulphated ash: <1.5%

b) Density : 1.492 g/cm3

c) Solubility: practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol
d) Viscosity: 4.86 Pa s (4860 cP) for a 1% w/v dispersion.

e) Solubility and storage condition: Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions.
f) Guar gum powder should be stored in a well-closed container in a cool, dry place.
g) The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methylparaben and 0.02% propylparaben as a preservative.

**Safety**

Guar gum is widely used in foods and oral and topical pharmaceutical formulations.

$LD_{50}$ (hamster, oral): 6.0 g/kg

$LD_{50}$ (mouse, oral): 8.1 g/kg

$LD_{50}$ (rabbit, oral): 7.0 g/kg

$LD_{50}$ (rat, oral): 6.77 g/kg

**Functional category**

Suspending agent; tablet binder; tablet disintegrant; viscosity increasing agent

**Application in pharmaceutical formulation or technology .**

1. Guar gum is widely used in oral and topical pharmaceutical formulations.

2. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and Disintegrant

3. Concentration upto 10 %w/w is used as tablet binder.

4. Guar gum is used as a suspending and thickening and stabilizing agent in in oral and topical formulations.
5. Guar gum is commonly used in cosmetics, food products, and pharmaceutical Formulations

6. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose.
7. Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus.

**5.2.3. KARAYA GUM:**

**SYNONYMS:** Karaya, gum karaya, *Sterculia*, gum *sterculia*, Kadaya, Katilo, Kullo, Kuterra;

**DEFINITION:**

A dried exudation from the stems and branches of *Sterculiaurens* Roxburgh and other species of *Sterculia*(Fam. *Sterculiaceae*) or from *Cochlospermumgossypium*A.P. De Candolle or other species of *Cochlospermum*(Fam. *Bixaceae*); consists mainly of high molecular-weight acetylated polysaccharides, which on hydrolysis yield galactose,rhamnose, and galacturonic acid, together with minor amounts of glucuronic acid.

**DESCRIPTION:**

Unground product: occurs in tears of variable size and in broken irregular pieces having a characteristic semi-crystalline appearance; pale yellow to pinkish brown; translucent and horny Powdered product: pale grey to pinkish brown; a distinctive odour of acetic acid. Items of commerce may contain extraneous materials such as pieces of bark which must be removed before use in food.Unground samples should be powdered to pass a standard ISO sieve of 355 µm (USA No. 45) and mixed well before performing any of the following tests.

**CHARACTERISTICS:**

**Solubility**: 2 g added to 50 ml of water swells to form a granular, stiff, slightly opalescent gel which is acid to litmus; insoluble in ethanol.

**Swelling by ethanol solution**: Karaya gum swells in 60% ethanol distinguishing it from other Gums.

**Colour reaction:** Boil 1 g of the sample with 20 ml of water until a mucilage is formed. Add 5 ml of hydrochloric acid and boil the mixture for 5 min. A permanent red or pink colour develops.

Warm 0.5 g of the sample with 2 ml of 5 M sodium hydroxide; a brown colour is produced.

**Precipitate formation:**

Shake 1 g of the sample with 80 ml of water for 24 h. Boil 4 ml of the resulting mucilage with 0.5 ml of concentrated hydrochloric acid, add 1 ml of 5 M sodium hydroxide and filter. To the filtrate add 3 ml of potassium cupric tartrate solution and heat. A red precipitate is formed.

**Gumconstituents:** Proceed as directed under *Gum Constituents Identification* using the following as reference standards: galactose, rhamnose, galacturonic acid, glucuronic acid, mannose, arabinose and xylose. Galactose, rhamnosegalacturonic acid, and glucuronic acid should be present and mannose, arabinose and xylose should be absent.

**PURITY**

**Loss on drying:** Not more than 20% (105o, 5 h) **Total ash:** Not more than 8%.

**Acid insoluble ash** : Not more than 1%

Weigh 3 g of the sample to the nearest 0.1 mg in a tared crucible. Ignite ata low temperature (about 550o), not to exceed a very dull redness, until free from carbon, cool in a desiccator, and weigh. If a carbon-free ash is not obtained, wet the charred mass with hot water, collect the insoluble residue on an ashless filter paper, and ignite, in the crucible, the residue and filter paper until the ash is white or nearly so. Add the filtrate, evaporate it todryness, and heat the whole to a dull redness. If a carbon-free ash is stillnot obtained, cool the crucible, add 15 ml of ethanol, break up the ash with a glass rod, burn off the ethanol, again heat the whole to a dull rednessand cool. Boil this ash with 25 ml of dilute hydrochloric acid TS for 5 min. Collect the insoluble matter on a tared Gooch crucible or ashless filter, wash with hot water, ignite, cool and weigh. Calculate the percentage of acid-insoluble ash from the weight of the sample.

**Uses**

- Karaya gum is used in cosmetics and food, and in pharmaceuticals as a laxative and adhesive
- Use as a bulk-forming laxative to treat constipation.
- Karaya gum is a sap-like material taken from a tree that grows in India. People use it to make medicine.
- Karaya gum is used as a bulk-forming laxative to relieve constipation. It is also used to increase sexual desire (as an aphrodisiac).
- In manufacturing, karaya gum is used as a thickener in medications, cosmetics, and denture adhesives; and as a binder and stabilizer in foods and beverages.

***How does it work?***

Karaya gum swells in the intestine, which stimulates the digestive tract to push stool through. Use as a bulk-forming laxative to treat constipation.

**Side effects:**

Karaya gum seems safe for most people when taken with plenty of fluids. It can block the intestines if you do not drink enough fluid.

***Special Precautions & Warnings:***

**Pregnancy and breast-feeding**: Not enough is known about the use of karaya gum during pregnancy and breast-feeding. Stay on the safe side and avoid use.

**Blockage in the intestine (bowel obstruction)**:

Don’t use any bulk-laxative, including karaya gum, if you have a bowel obstruction.

Medications taken by mouth (Oral drugs) interacts with karaya gum **Interactions:**

Karaya contains a type of soft fiber called mucilage. Mucilage can decrease how much medicine the body absorbs. Taking karaya at the same time you take medications by mouth can decrease the effectiveness of your medication. To prevent this interaction take karaya at least one hour after medications you take by mouth.

**Dosing:**

The appropriate dose of karaya gum depends on several factors such as the user's age, health, and several other conditions. At this time there is not enough scientific information to determine an appropriate range of doses for karaya gum. Keep in mind that natural products are not always necessarily safe and dosages can be important. Be sure to follow relevant directions on product labels and consult your pharmacist or physician or other healthcare professional before using.

### 5.2.4. XANTHAN GUM:

**Synonyms :**

Corn sugar gum; Merezan; Rhodigel.

**Chemical Name :**

Xanthan gum

**Molecular weight:**

$2X10^6$(approximately)

**Functional category :**

Stabilizing,suspending,andviscositybuilding agent.

**Application:**

It iswidely used as suspending, thickening, stabilizing and emulsifying agent. It is also used to prepare sustained-release matrix tablets.

**Description:**

It occurs as a cream or white colored odorless free flowing fine powder.

**Solubility:**

Practically insoluble in ethanol and ether; soluble in cold and warmwater.

**Viscosity:**

1200-1600 mPa s for 1% w/v aqueous solution

**Incompatibility:**

It incompatible with cationic surfactants, polymers, preservatives, oxidizing agents, Sod. CMC, Verapamil.

**Stability and storage condition:**

Stable material at wide range of pH and temperature. It should be stored in a well closed container in a cool, dry place.

**Safety:**

It regardedas nontoxic and nonirritant at the level employed as pharmaceutical excipient.

## 6. MATERIALS AND METHODS

### MATERIALS:

The following materials of Pharma grade or the best possible Laboratory Reagent

(LR) were used as supplied by the manufacturer. Distilled water was used in all experiments.

**Table 6.1: List of chemicals used with grade and supplier**

| Sl. no. | Materials used | Grade | Manufacturer |
|---|---|---|---|
| 1. | Nicardipine | Pharma grade | Mylan Laboratories |
| 2. | Sodium alginate | LR | Loba chemie Pvt. Ltd., Mumbai |
| 3. | Xanthan gum | LR | Loba chemie Pvt. Ltd., Mumbai |
| 4. | Guar gum | LR | Loba chemie Pvt. Ltd., Mumbai |
| 5. | Karaya gum | LR | Loba chemie Pvt. Ltd. Mumbai |
| 6. | Calcium chloride | LR | Loba chemie Pvt. Ltd. Mumbai |

**Table 6.2: List of instruments used**

| Sl. No. | Instrument | Manufacturer |
|---|---|---|
| 1. | UV visible spectrophotometer | PG Instruments, T60 UV visible spectrophotometer |
| 2. | FTIR spectrophotometer | IR-Affinity-1, Shimadzu, Japan. |
| 3. | Mechanical stirrer (electric motor) | Pilot , India |
| 5. | Vernier caliper | Samata enterprises |
| 6. | SEM, JSM – 8400A | JEOL, Japan. |
| 7. | Digital balance | N.S. Scientific supplies, Mysore |
| 8. | Digital pH meter | N.S. Scientific supplies, Mysore |
| 9. | Melting point apparatus | Ganga scientific works, Bangalore |
| 10 | Hot plate | Ganga scientific works, Bangalore |
| 11. | USP dissolution XXIII apparatus | Labindia DS8000 |

## METHODS:

### Preformulation studies:[66-69]

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

### Solubility:

Solubility of Nicardipine was determined in water, pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Nicardipine in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41.
The filtered solutions were analyzed spectrophotometrically at 354 nm.

### Determination of λmax:

A solution of Nicardipine containing the concentration 10 µg/ ml was prepared in 6.8pH buffer and UV spectrum was taken using Shimadzu (UV-2550) double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

### Calibration curve of Nicardipine in 0.1NHCL:

10mg of Nicardipine was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 0.1 N HCL to get 2 to 12 µg/ml of. The absorbance of the solution was measured against 0.1 N HCL as blank at 354 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

### Calibration curve of Nicardipine in 6.8pH phosphate buffer:

10mg of Nicardipine was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 6.8pH phosphate buffer to get 2 to 12 µg/ml of. The absorbance of the solution was measured against 6.8pH phosphate buffer as blank at 354 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

**Drug polymer interaction (FTIR) study**

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2 mg of Nicardipine alone, mixture of drug and polymer, beads were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 400–4000 cm-1 was recorded taking air as the reference and compared to study any interference.

**FORMULATION DESIGN:**

**Table 6.3.1 Formulation design for Nicardipine hydrogel beads using different ratios of drug and polymers.**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nicardipine** | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| **Sodium Alginate** | 500 | 1000 | 1500 | 500 | 1000 | 1500 | 500 | 1000 | 1500 | 1000 | 1000 |
| **Karaya gum** | 500 | 750 | 1000 | - | - | - | 500 | 750 | 750 | 750 | 750 |
| **Guar gum** | - | - | - | 500 | 750 | 1000 | 500 | 750 | 1000 | 1000 | 1000 |
| **Drug+Polymer ratio** | 1:1 | 1:1.5 | 1:2 | 1:1 | 1:1.5 | 1:2 | 1:1:1 | 1:1.5:1.5 | 1:1.5:2 | 1:1.5:2 | 1:1.5:2 |
| **Calcium chloride (%w/v)** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 3 |

**Preparation of Nicardipine Hydro gel beads:**

**Method used – Ionotropic gelation method:**

Accurate quantity of polymer was dissolved in 25ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution, it should be stirred until a homogenous mixture was obtained. The mixture was extruded through a 23G syringe needle into calcium chloride solution (2% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight.

## EVALUATION OF NICARDIPINE HYDROGEL BEADS[67-75]

### Surface morphology (SEM) :

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry Nicardipine gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Nicardipine hydrogel beads were taken by random scanning of the stub.

### Percentage yield:

Percentage practical yield of Nicardipine hydrogel beads was calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Nicardipine beads recovered from each batch in relation to the sum of starting material.
The percentage yield of Nicardipine beads prepared was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

### Drug Content:

To determine the drug content and encapsulation efficiency of the beads, 20 mg weight equivalent hydrogel beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent. The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent , and drug content assayed using a UV-visible spectrophotometer at λmax of 210 nm.

### Drug Entrapment Efficiency;

The drug entrapment efficiency of prepared beads was determined by using the following equation.

—
EE (%) = Actual Drug Content/ Theoretical Drug Content X 100

### *In-vitro* dissolution studies:

#### *Procedure for In-vitro dissolution study:*

The release rate of Nicardipine Hydrogel beads was determined by employing USP XXIII apparatus I (basket method). The dissolution test was performed using 900 ml 0.1N HCL, for 2hours and at 6.8pH buffer for remaining hours, iat 37 ±0.5°C at 50 rpm. Nicardipine hydro

gel beads equivalent to 20 mg of Nicardipine was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 354 nm.

**Kinetics of drug release**[76:]

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q0-Q) v/s t], Higuchi's square root of time (Q v/s $t_{1/2}$ ) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t. In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

## 7. RESULTS AND DISCUSSION

### 7.1 PREFORMULATION STUDIES

**Solubility study:**

**Table : Solubility studies of Nicardipine**

| Solvent | Solubility (µg/ml) |
|---|---|
| 0.1N HCl | 0.150 |
| 6.8 pH buffer | 0. 889 |
| 7.4pH buffer | 0.331 |
| Water | 0.122 |

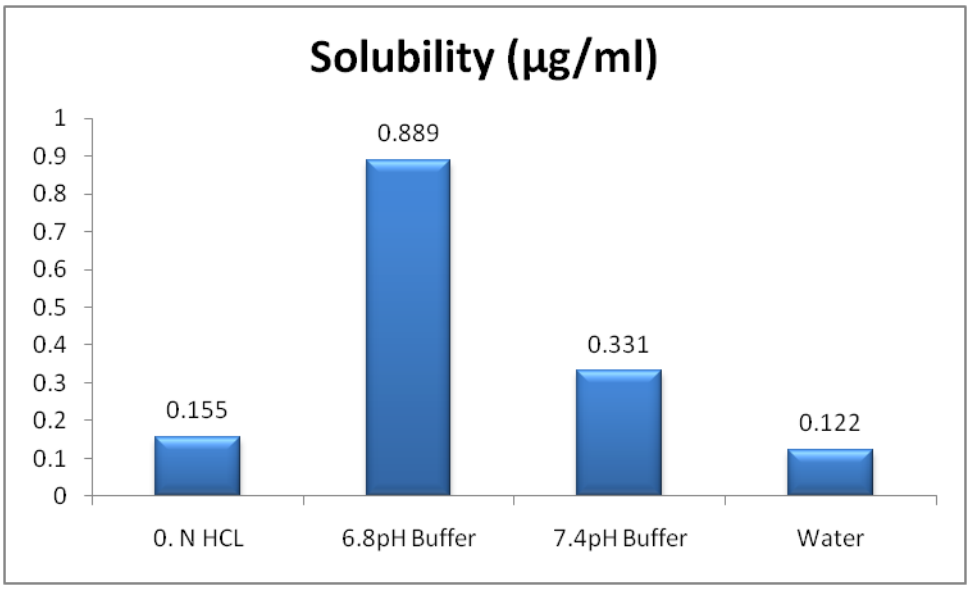



**Fig: Solubility studies of Nicardipine**

**Discussion:** The solubility of Nicardipine was occurs more on 6.8 pH phosphate buffer with compare of 7.4 pH phosphate buffer and 0.1 N HCl solution

**Determination of λmax:**

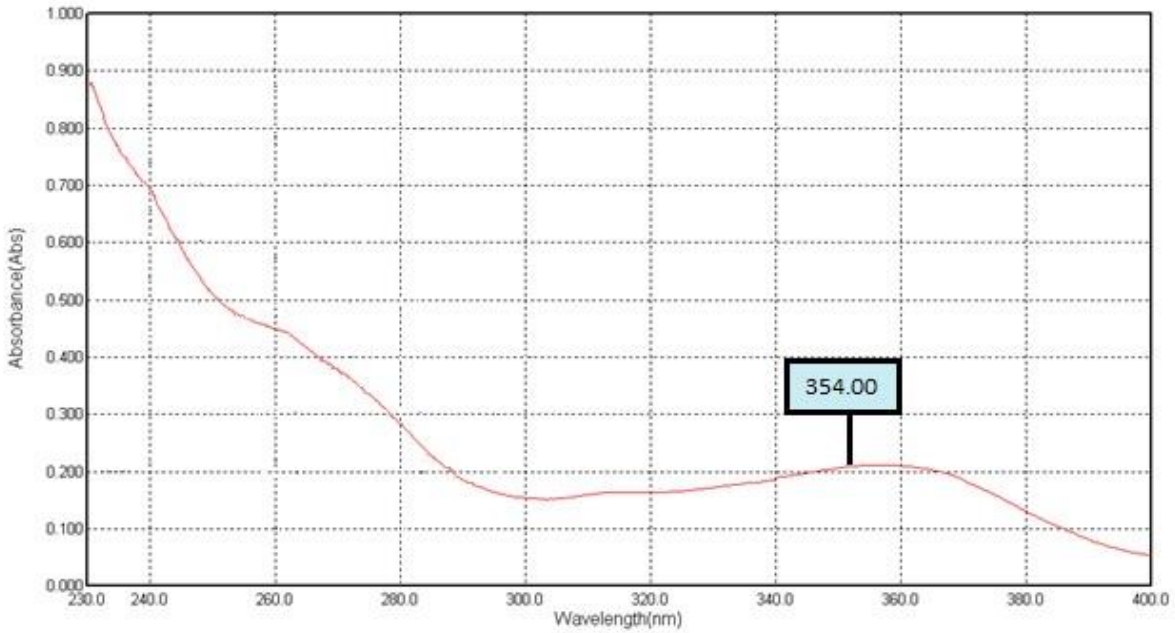



**Fig 7.1 λmax of Nicardipine in 6.8pH buffer (10µg/ml)**

**Discussion:**

A solution of Nicardipine containing the conc. 10 µg/ ml was prepared in 6.8pH buffer and UV spectrum was taken using PG Instruments T60 double beam spectrophotometer.

The solution was scanned in the range of 200 – 400 nm. The maximum absorbance was found to be at 354 nm.

### 7.2. Calibration curve of Nicardipine at λmax of 354 nm

**Table 7.2 Standard calibration data of Nicardipine in 6.8pH buffer**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.149 |
| 4 | 0.272 |
| 6 | 0.397 |
| 8 | 0.515 |
| 10 | 0.639 |
| 12 | 0.765 |

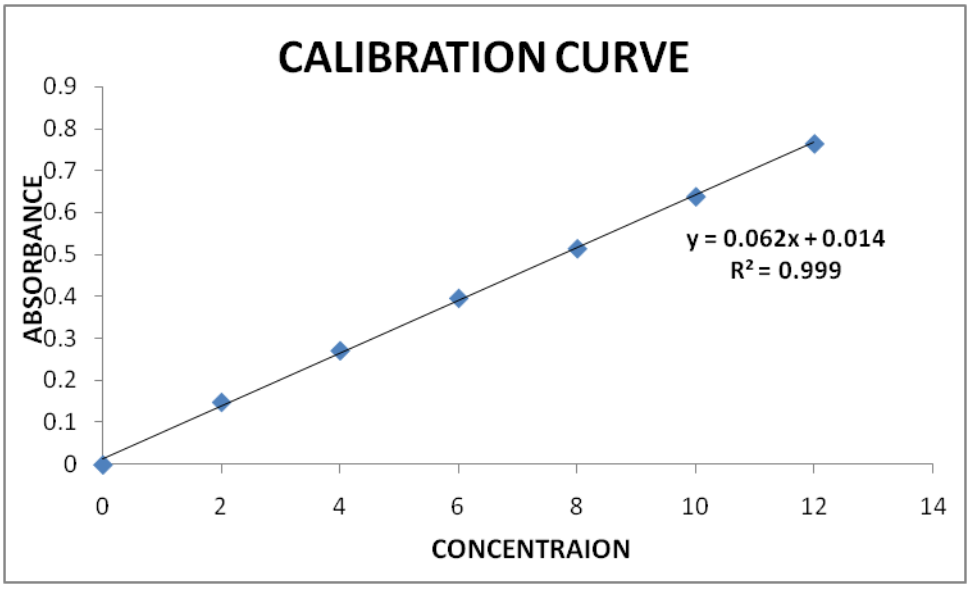



**Fig7.2 Standard calibration curve of Nicardipine in 6.8pH buffer**

**Discussion:**

The linearity was found to be in the range of 5-30µg/ml in pH 6.8 buffer and 0.1N HCl. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

**Table 7.2 Standard calibration curve of Nicardipine with7.4 pH phosphate buffer**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.142 |
| 4 | 0.252 |
| 6 | 0.392 |
| 8 | 0.535 |
| 10 | 0.659 |
| 12 | 0.766 |

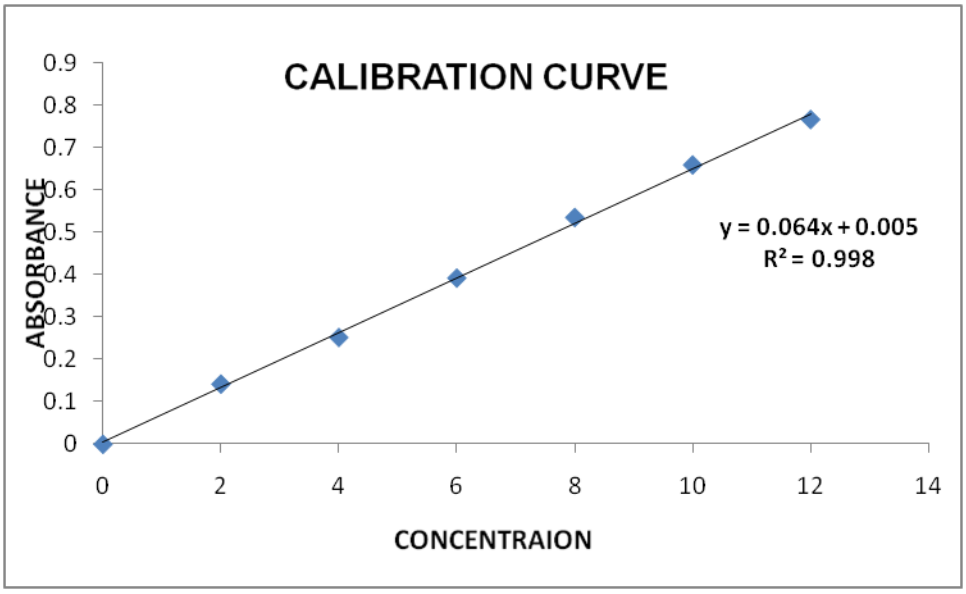



**Fig7.2 Standard calibration curve of Nicardipine in 7.4 pH phosphate buffer**

## 7.2 EVALUATION OF NICARDIPINE HYDROGEL BEADS

### 7.2.1 Drug polymer interaction (FTIR) study

From the spectra of Nicardipine, and optimized formulation, it was observed that all characteristic peaks of Nicardipine were present in the combination spectrum, thus indicating compatibility of the Drug and polymer.

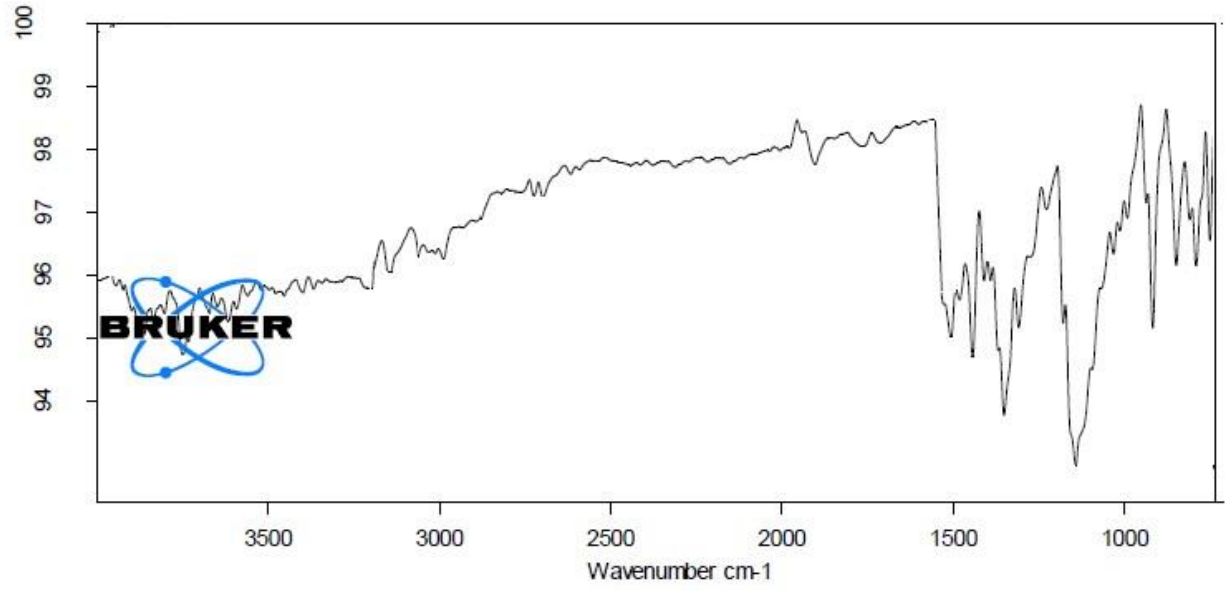



**Fig 7.3 Fig: FTIR studies of pure drug**

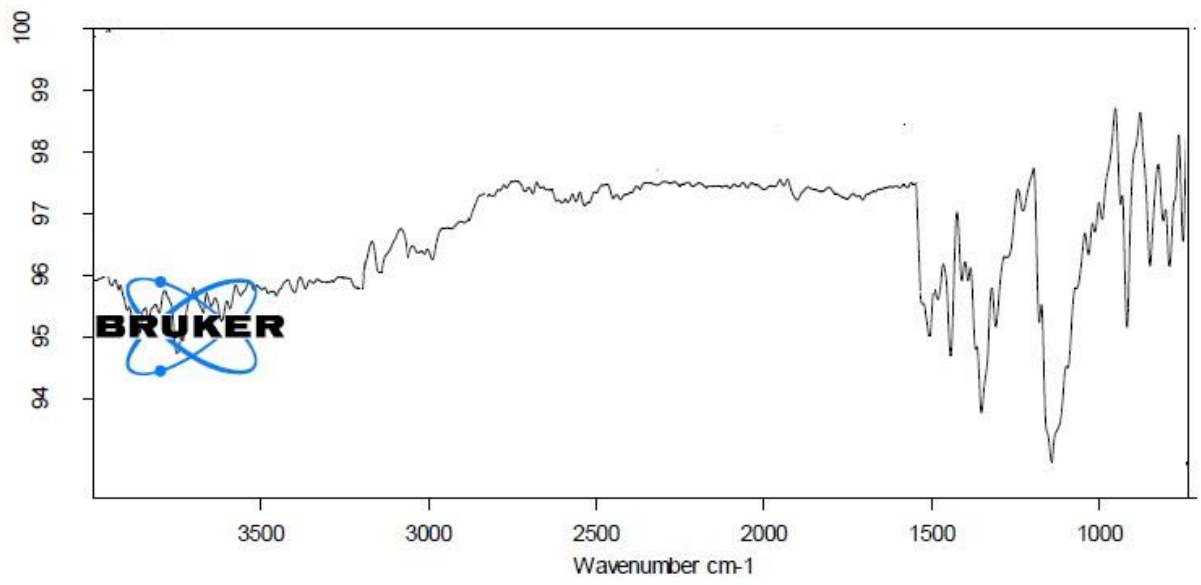



**Fig 7.4,FTIR studies of drug+ Excepients**

**Discussion:**

From the compatibility studies it was concluded that the functional groups that were present in the pure drug were also found in the optimized formulation with very minute changes, from this we can conclude that the drug and excipients have no interactions.

### 7.2.2 Surface morphology - Scanning Electron Microscopy (SEM)

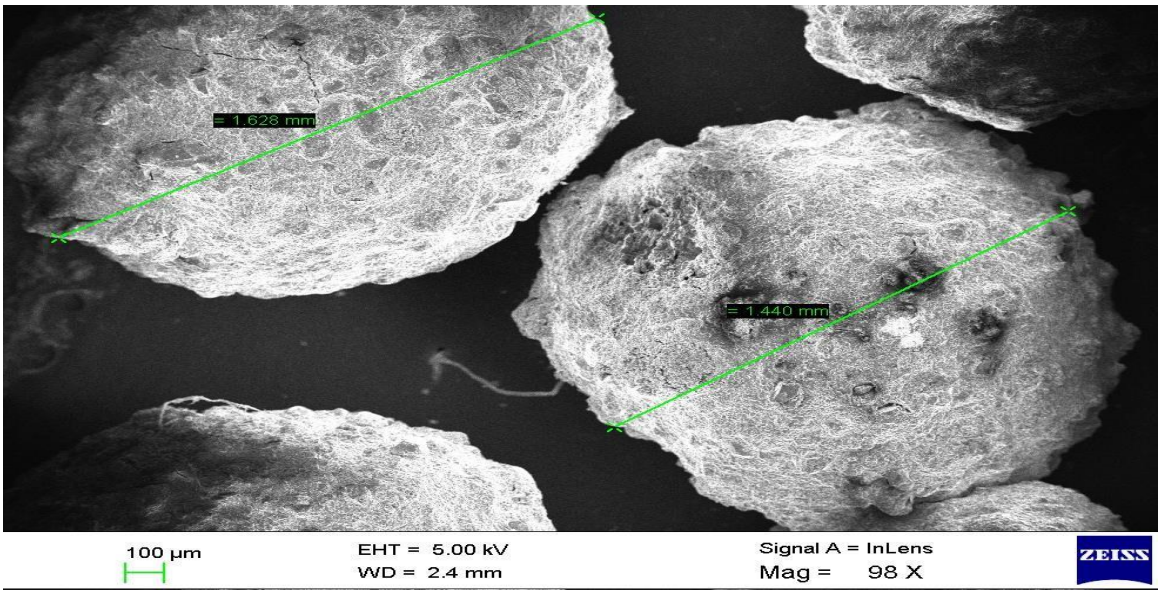



**Fig 7.5 SEM photographs of Hydrogel beads**

**Table 7.5.1 Drug Content and Percentage yield of Nicardipine Hydrogel beads**

| Formulation Code | Percentage Yield | Drug content (%) |
|---|---|---|
| **F1** | 81.56 | 94.36 |
| **F2** | 85.49 | 95.48 |
| **F3** | 92.36 | 96.02 |
| **F4** | 94.18 | 99.62 |
| **F5** | 85.46 | 96.16 |
| **F6** | 92.49 | 98.42 |
| **F7** | 90.75 | 95.35 |
| **F8** | 82.65 | 96.72 |
| **F9** | 88.35 | 98.76 |
| **F10** | 96.44 | 93.75 |
| **F11** | 91.54 | 96.86 |

**Discussion:**

The percentage yield of all formulation was found in the range of 80.65 to 94.44%. The drug content estimations showed the values in the range of 93.75 to 99.62% which reflects good uniformity in drug content among the formulations F1 to F11 and indicates these values were within specified range as per USP (±15% of label claim was acceptable).

### 7.2.6 *In vitro* dissolution studies:

**Table 7.6 *In vitro* release data of Hydrogel beads of Nicardipine**

| Time (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** | 0 | 0 |
| 1 | 34.86 | 33.74 | 22.63 | 30.18 | 27.43 | 18.86 | 18.86 | 12.06 | **8.63** | 22.22 | 12.66 |
| 2 | 40.18 | 44.25 | 29.36 | 35.47 | 34.05 | 24.48 | 28.63 | 25.53 | **15.49** | 29.12 | 18.45 |
| 3 | 54.08 | 58.32 | 38.96 | 39.05 | 46.75 | 36.75 | 36.18 | 28.34 | **20.76** | 33.78 | 26.98 |
| 4 | 62.48 | 64.04 | 44.36 | 48.18 | 52.05 | 46.86 | 44.32 | 32.48 | **28.43** | 42.87 | 38.94 |
| 5 | 75.49 | 76.36 | 56.42 | 53.48 | 58.78 | 48.36 | 57.36 | 45.12 | **39.05** | 54.35 | 44.64 |
| 6 | 89.49 | 85.09 | 69.89 | 68.02 | 64.63 | 54.53 | 64.75 | 54.04 | **42.01** | 69.99 | 56.12 |
| 7 | 97.05 | 90.75 | 78.63 | 74.05 | 69.18 | 66.31 | 72.49 | 63.18 | **56.02** | 76.64 | 60.09 |
| 8 | | 95.35 | 85.36 | 88.34 | 78.06 | 72.05 | 82.05 | 77.49 | **68.05** | 89.87 | 75.97 |
| 9 | | | 92.31 | 97.56 | 89.52 | 85.49 | 96.43 | 85.36 | **78.43** | 99.77 | 78.64 |
| 10 | | | 98.73 | | 95.35 | 93.36 | | 92.75 | **85.49** | | 85.66 |
| 11 | | | | | | 98.72 | | 97.63 | **95.36** | | 88.36 |
| 12 | | | | | | | | | **99.45** | | 91.23 |

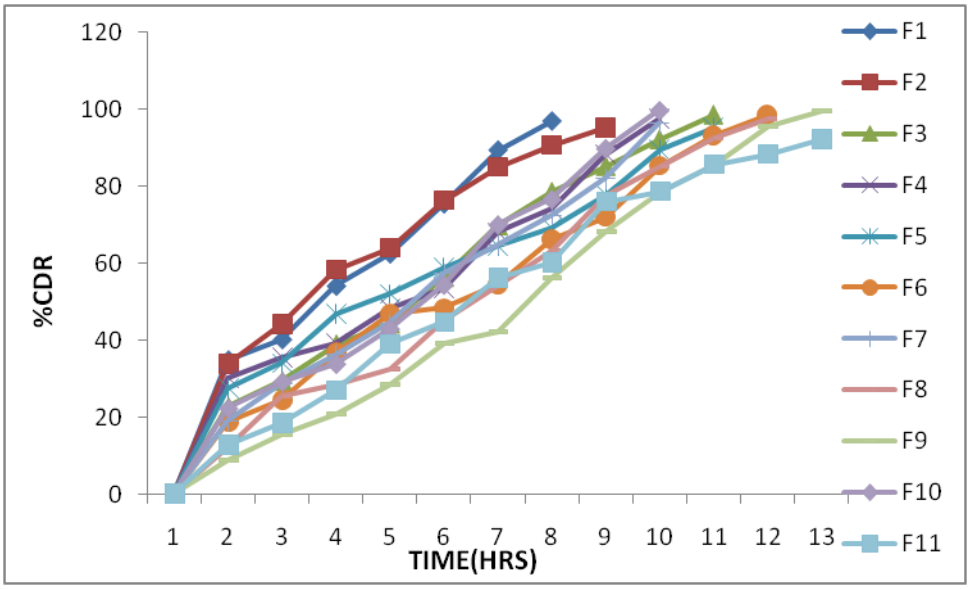



**Fig 7.6:%DR of F1-F11**

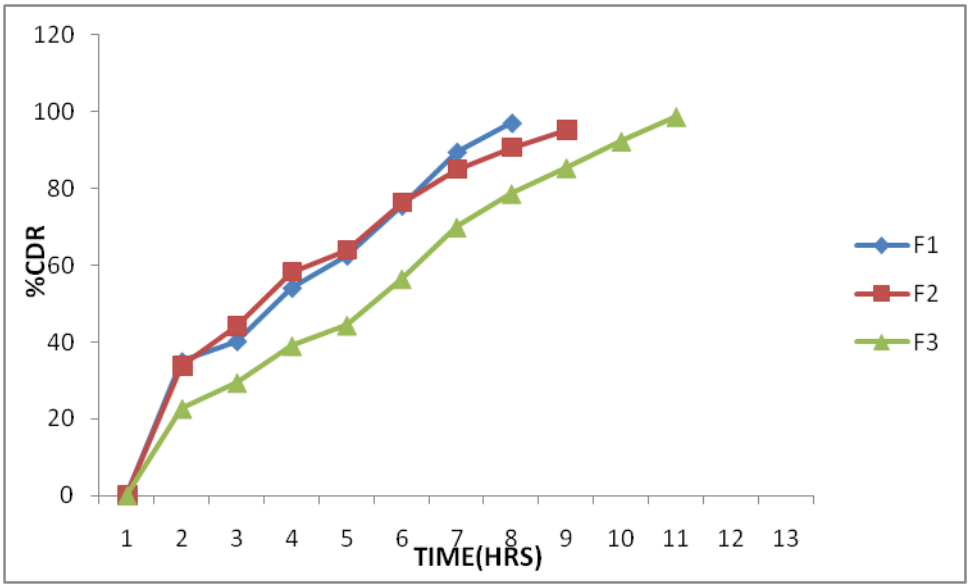



**Fig 7.7:%DR of F1-F3**

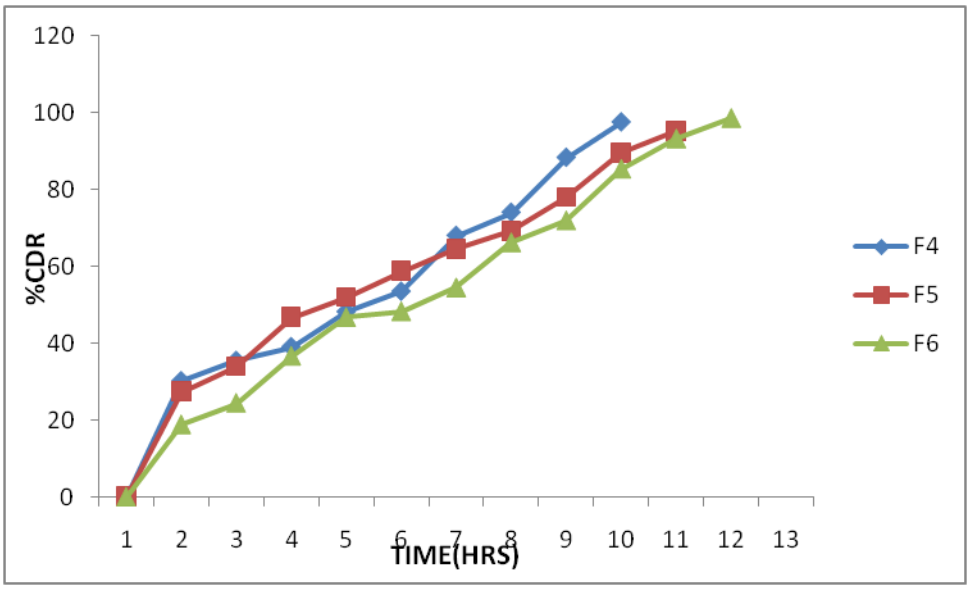



**Fig 7.8:%DR OF F4-F6**

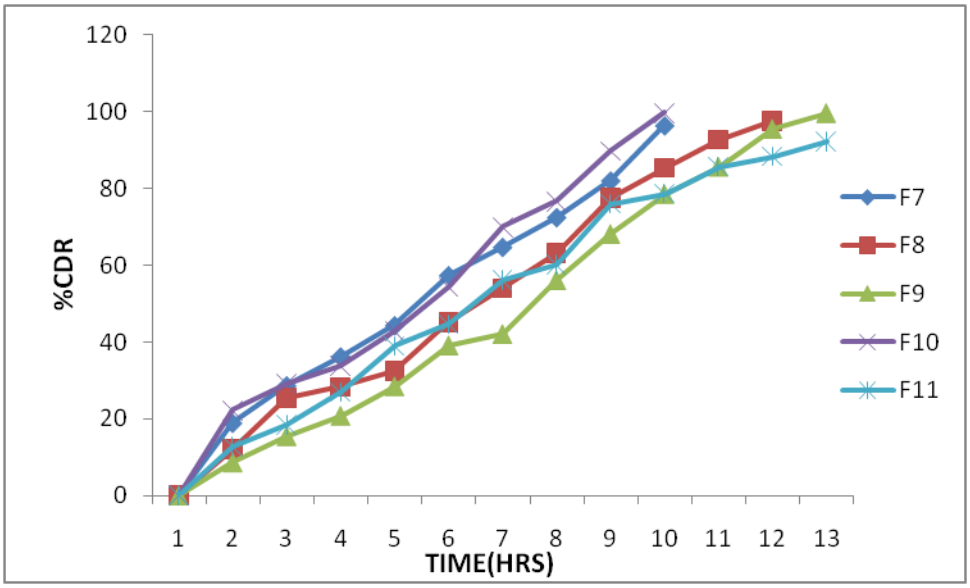



**Fig 7.9 :%DR OF F7-F11**

**Discussion:**

The *in vitro* performance of Nicardipine hydrogel beads showed prolonged and controlled release. The results of the *in vitro* dissolution studies shows controlled and predictable manner as the polymer concentration increases the drug release from the hydrogel beads decreases. Among all the three polymers used for formulation of hydrogel beads of Nicardipine, the formulations prepared by using Karaya gum & guar gum at 1:1.5:2 ratio shows maximum drug release at the end of 12hrs.

So F9 formulation was considered as the optimized formulation, the drug release kinetics were performed for the F9 formulation.

**DRUG RELEASE KINETICS:**
**ZERO ORDER (F9)**

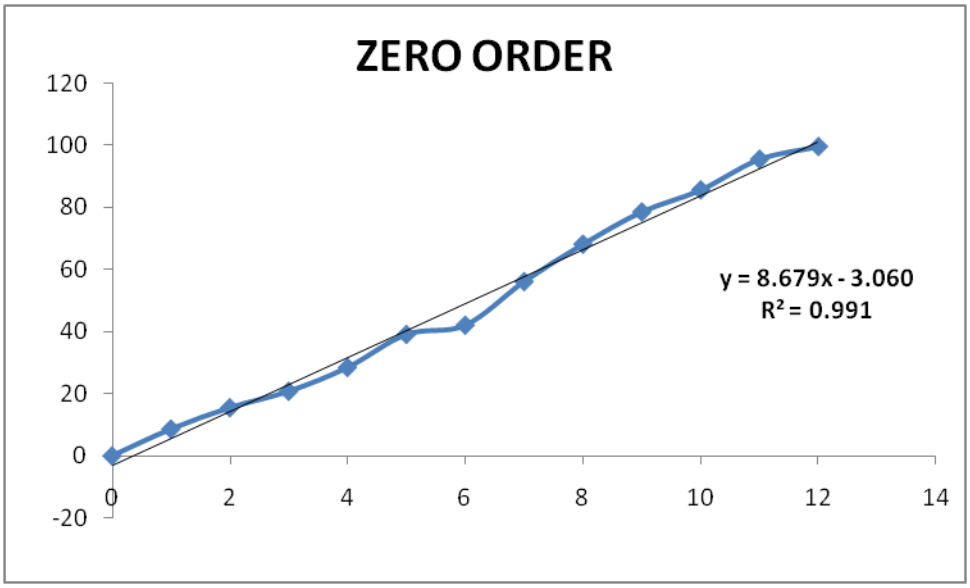



**Fig 7.10: Zero order graph of optimized formulation FIRST ORDER (F9)**

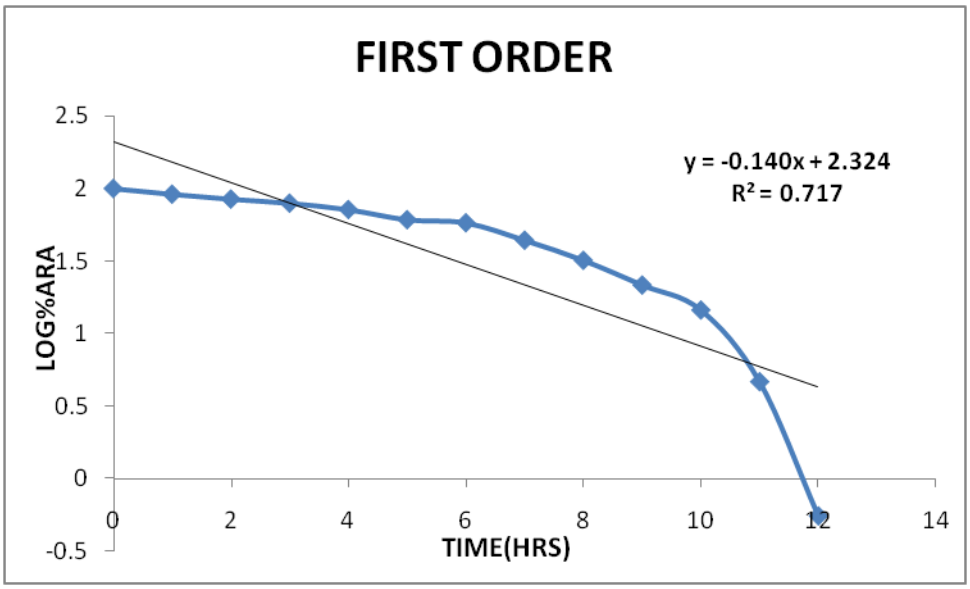



**Fig 7.11: First order graph of optimized formulation HIGUCHI PLOT (F9)**

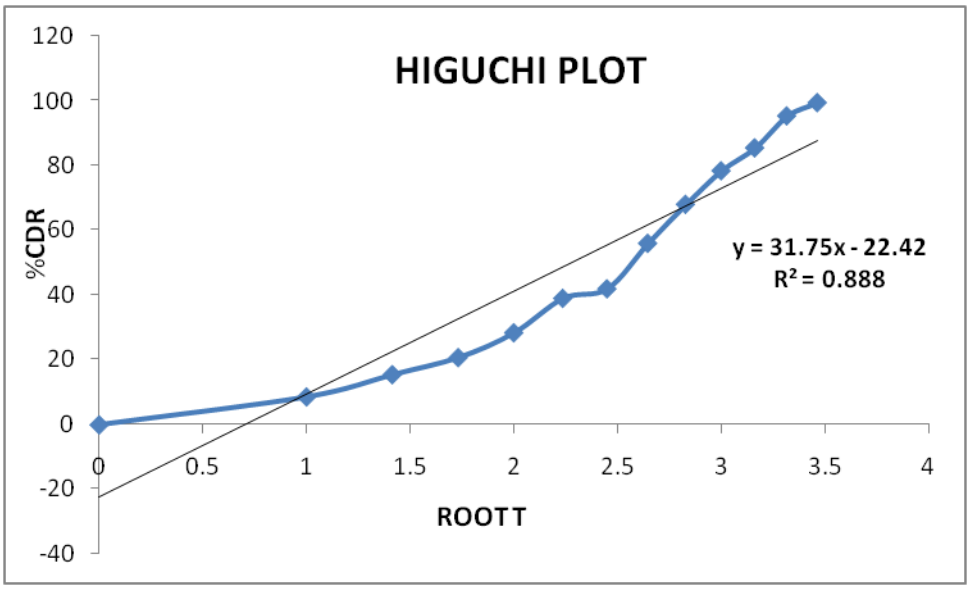



**Fig7.12: Higuchi plot of optimized formulation PEPPAS PLOT (F9)**

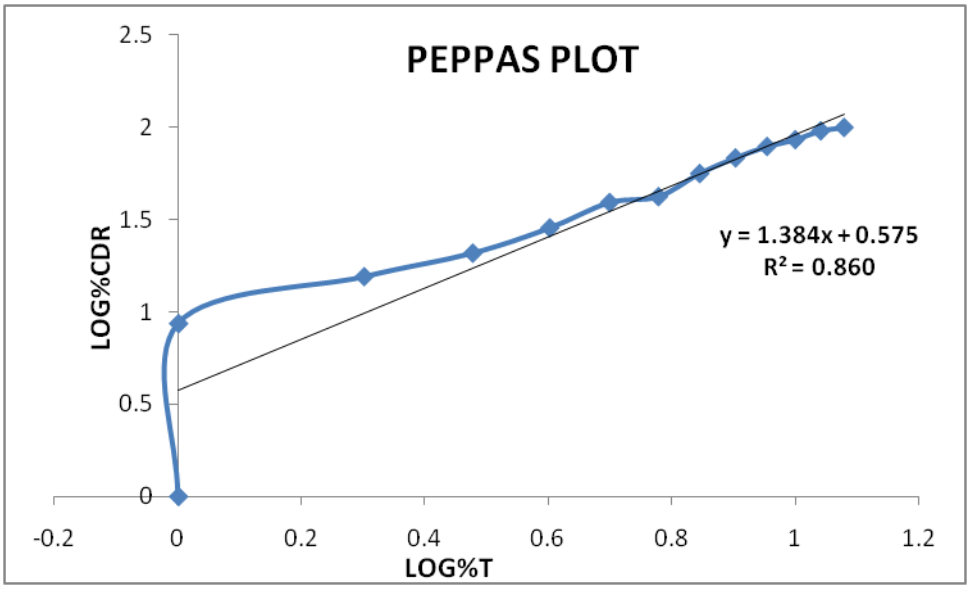



**Fig 7.13: peppas plot of optimized formulation**

## 7.3. DRUG RELEASE KINETICS:

**Table 7.7: Drug Release Kinetics:**

| Batch | Zero Order | First Order | Higuchi | Peppas | Peppas (n) |
|---|---|---|---|---|---|
| **F9 ($r^2$)** | 0.991 | 0.717 | 0.888 | 0.860 | 1.384 |

From the drug release kinetics of the Nicardipine hydrogel beads it was concluded that the formulation F9 follows Zero order release with super case II transport mechanism.

## 9. SUMMARY AND CONCLUSION

The goal of the present work is to formulate controlled release hydrogel beads using Nicardipine as a model drug on the various parameters including the *in vitro* release kinetics. It is highly soluble in 6.8 pH, which makes Nicardipine as a suitable candidate for formulating hydrogel beads in order to prolong the drug release to improve its bioavailability.

An attempt was made to prepare hydrogel beads of Nicardipine by using sodium alginate and rate retarding natural polymers like karaya gum, xanthan gum and guar gum. In the present study eleven formulations were formulated by using ionotropic gelation method.

In pre formulation study, estimation of Nicardipine was carried out by PG Instruments T60 UV spectrophotometer at $\lambda_{max}$ (354nm) using 6.8 pH buffer as solvent, which had a good reproducibility and this method was used throughout the study.

All the formulations were subjected for preformulation evaluation. Results of preformulation studies, FTIR, SEM, particle size and size distribution, % yield, drug content, buoyancy time, entrapment efficiency, *in vitro* dissolution and release kinetics.
The FTIR Spectra revealed that, there was no interaction between polymers and Nicardipine.

Entrapment efficiency was increased with increased in polymer concentration. From the results it can be inferred that there was a proper distribution of Nicardipine in the beads and the deviation was within the acceptable limits.

On the basis of release data and graphical analysis formulation Nicardipine showed a good controlled release profile with maximum entrapment efficiency because of high polymer concentration (xanthan gum) with sodium alginate than other polymers. The invitro dissolution data for best formulation **F9** were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F9 shows $R^2$ value 0.991. As its value nearer to the '1' it is conformed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot,The 'n' value is 1.384 for the optimised formulation (**F9**) i.e., n value was >0.89 this indicates Super case transport.

Hence, from the above obtained data it can be summarized that it is possible to formulate hydrogel beads to achieve a controlled release using sodium alginate and karaya gum and guar gum.

## 11.REFERENCES

1. Patel MG, Patel RH, Patel M, Patel KJ. Floating drug delivery system: An innovative approach to prolong gastric retention. Available at www.pharmainfo.net.aug.2010.
2. Garg R, Gupta GD. Progress in controlled gatroretentive delivery systems. Tropical J Pharm Res 2008;7(3):1055- 66.
3. Ashford M. The gastrointestinal physiology and drug absorption. In: Pharmaceutics the science of dosage form design. Aulton ME, editor. Pharmaceutics the science of dosage form design. 2nd ed. Edinburgh: Churchill living stone. 2004; 220.

4. Wilson KR, Waugh A. Anatomy and physiology in health and illness, 9th ed.London: Churchill Livingstone; 1996.
5. Wilson CG, Washington N. The stomach: its role in oral drug delivery.Physiological Pharmaceutical: Biological Barriers to Drug Absorption. Chichester, UK: Ellis Horwood;1989:47-70.
6. Wong DSL. Prolonged release active agent dosage form adapted for gastric retention. US Patent 2000; 15th Sept: 120-803.
7. Yuveraj Singh T, Naruk PS, Ojha GR. Development and evaluation of floating microspheres of Verpamil Hydrochloride. Braz J pharma sci 2007;43(4):529-34.
8. Gattani YS, Kawtikwar PS, Sakarka DM. Formulation and evaluation of gastro retentive multiparticulate drug delivery system of Aceclofenac. Int J ChemTech Res 2009;1(1):1-10.
9. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: Need and development. Indian J pharma Sci 2005;67(3):265-72.
10. Timmermans J, Moes AJ. Floating dosages forms: A Review. Int J Pharm1990;62:207-16.
11. Garima, Chawla, Piyush. Gupta, Vishal. Koradia, Bansal KA. Gastro retention: A Means to address regional variability in intestinal drug absorption. Pharm tech 2003;27(2):50-68.
12. R.Talukder and R.Fissihi. Gatroretentive Delivery Systems: A Mini review. DrugDev Ind Pharmacy 2004;30(10):1019-28.
13. Xu.WL, Tu.XD, Lu.ZD. Development of Gentamycin sulfate sustained-release tablets remaining-floating in stomach. Yao Hsueh Pao 1991;26(7):541-45.
14. Jain NK. Progress in controlled and novel drug delivery systems, Ist ed. NewDelhi: CBS Publishers; 2004.
15. Srivastava AK, Narayanarao D. Floating microspheres of Cimetidine: formulation, characterization and in- vitro evaluation. Acta Pharm 2005;55:277-85.
16. Gansbeke BV, Timmermans J, Schoutens A, Moes AJ. Intragastric positioning of two concurrently ingested pharmaceutical matrix dosage forms. Nucl Med Biol 1991;18:711-18.
17. Fursule RA, Patra CN, patil GB, Kosalge SB, patil PO, Deshmukh PK. Study of multiparticulate floating drug delivery system prepared by emulsion gelation technique. Int J Chem Tech Res 2009;1(2):162-7.
18. Kumaresh SS, Tejraj MA, Sunil AA, Nadagouda NM, Padmakar VK. Effect of coexcipient on drug release and floating property of Nifedipine hollow microspheres: a novel gastro retentive drug delivery system. J Appl Polym Sci 2006;100:486-94.
19. Jimenez-Castellanos NR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1993;19:143.
20. Urguhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US patent 4 434 153. February 28, 1994.
21. Jain AK, Jain CP, Tanwar YS, Naruka, PS. Formulation characterization and in vitro evaluation of floating microspheres of Famotidine as a gastro retentive dosage form. Asian J Pharm 2009;3(3):222-6

22. Basavaraj BV, Deveswaran R, Bharath S, Abraham S, Furtado S, Madhavan V. hollow microspheres of Diclofenac Sodium a gastro retentive controlled delivery system. Pak J Pharm Sci 2008;21(4):451-4.
23. Gronia R, Heun G. Oral dosage forms with controlled gastrointestinal transit.Drug Dev Ind Pharm 1984;10:527-39.
24. Atyabi F, Sharma HL, Mohammad H, Fell JT. In vivo evaluation of a novel gatroretentive formulation based on ion exchange resins. J Cont Rel 1996;42:105-13.
25. Vyas SP, Khar RK. Controlled drug delivery: Concepts and advances. 1st ed. NewDelhi: Vallabh Prakashan; 2002.
26. Klausner A, Lavy E, Friedman M, Hoffman A. Expandable gatroretentive dosage form. J Cont Rel 2003;90:143-62.
27. Singh BN, Kim HK. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Cont Rel 2000;63:235-7.
28. Whitehead L, Collett JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. Int J Pharm 2000;210:45-9.
29. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microbaloons) with acrylic resins containing Tranilast and their drug release characteristics (in vivo). J Cont Rel 1991;16:279-90.
30. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS Pharm Sci Tech 2005;6:372-90.
31. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Res J Pharm Tech 2008;1(4):345-48.
32. Shahaa SH, Patelb JK, Pundarikakshudua K, Patel NV. An overview of a gastro- retentive floating drug delivery system .Asian J Pharm Sci 2009;4 (1): 65-80.
33. www. Ditonline.info. Accessed on Aug 2010
34. Vaibhav J, Pravin Kumar B. Gastroretentive drug delivery system: Current approaches. J Pharm Res 2009;2(5):881-86.
35. Jain SK, Jain NK, Agarwal GP. Gastro retentive floating drug delivery: Drug delivery technology. 2005;5(7):1-9.
36. Sunil KJ, Govind PA, Narendra KJ. Evaluation of porous carrier-based floating Orlistat microspheres for gastric delivery. AAPS Pharm Sci Tech 2006;7(4):90.
37. Oth M, Franz M, Timmermans J, Moes A: The bilayer floating capsule: a stomach directed floating drug delivery system for Misprostal. Pharma Res 1992;9:298-302.
38. Menon A, Ritschel WA, Sakar A. Development and evaluation of a monolithic floating dosage form for Furosemide. J Pharm Sci 1994;83:239-45.
39. Kundlik MG, Ranju SP, Hitesh BG. Celecoxib loaded microbeads: A targeted drug delivery for colorectal cancer . International Journal of Current Pharmaceutical Research. 2010; 2(1):46-55.
40. Patent Number: 0563876: Biodegradable microbeads for the pharmaceutical and cosmetic uses; Issue Date: 1993.10.06.
41. Manjanna KM, Shivakuma B, Pramod kumar TM. Formulation of oral sustained release aceclofenac sodium microbeads. International Journal of PharmTech Research. 2009;1(3), 940-952.

42. Manjusha R, Anuja A, Yuvraj singh N. Review: Chitosan based hydrogel polymeric beads – As drug delivery system. Bioresources.2010;5(4):2765-2807.
43. Pornsak Sriamornsak, Nartaya Thirawong, Satit Puttipipatkhachorn. Morphology and Buoyancy of Oil-entrapped Calcium Pectinate Gel Beads. The AAPS Journal. 2004; 6 (3):1-7.
44. Patil JS, Kamalapur MV, Marapur SC, Kadam DV. Ionotropic gelation and polyelectrolyte complexation: The novel techniques to design hydrogel particulate sustained, modulated drug delivery system: A Review. Digest Journal of Nanomaterials and Biostructures . 2010; 5(1): 241 – 248.
45. Durga J, Arundhati B, Indranil kumar Y, Hari pratap S, Dinesh Chandra, Jain DA. Formulation and Evaluation of oil entrapped floating alginate beads of RanitidineHydrochloride.
International Journal of Pharmacy and Pharmaceutical Sciences.2009; 1(1):128-140.
46. Available at http://www.espace.library.uq.edu.au/view/UQ:266522.
47. Shiva Kumar Yellanki and Naveen Kumar Nerella. Stomach Specific Drug Delivery of Riboflavin using Floating Alginate Beads. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2 (2):160-162.
48. Patel RP, Baria AH, Pandya NB. Stomach-specific Drug Delivery of Famotidine using Floating Alginate beads. International Journal of PharmTech Research.2009; 1(2):288291.
49. Shishu, Neeta Gupta, Nidhi Aggarwal. Stomach-Specific Drug Delivery of 5- Fluorouracil Using Floating Alginate Beads. AAPS PharmSciTech. 2007; 8 (2):1-7.
50. S Takka et al et al, Formulation and evaluation of nicardipine HCl-alginate gel beads with factorial design-based studies, 6(3):241-6,1998.
51. Ya-Ni Dai etal, A novel pH sensitive N-succinyl chitosan/alginate hydrogel bead for nifedipine delivery,29(3), 173-184,2008.
52. Xu-Jiang Zhu etal, Pharmacokinetics of a novel nifedipine and pH-sensitive N-succinyl chitosan/alginate hydrogel bead in rabbits,36(12), 1463-1468,2010.
53. Shivhare UD etal, formulation and evaluation of hydrogel beads for sustained delivery of nifedipine, 3(3), , 267-275,2012
54. Ya-Ni Dai etal , Swelling characteristics and drug delivery properties of nifedipine-loaded pH sensitive alginate–chitosan hydrogel beads, 86B(2), 493-500,2008.
55. Sevgi Takka etal, Formulation and investigation of nicardipine HCl-alginate gel beads with factorial design-based studies, 6(3):241-6,1998.
56. Sanjay K. Jain.,Design and Development of Hydrogel Beads for Targeted Drug Delivery to the Colon, satranidazole. AAPS PharmSciTech 2007; 8 (3)
57. K.M. Manjanna.et.al.,Formulation and Optimization of Natural Polysaccharide Hydrogel Microbeads of Aceclofenac Sodium for Oral Controlled Drug Delivery, American Journal of Medical Sciences and Medicine, 2013, Vol. 1, No. 1, 5-17.
58. Pitta. Lavanya.et.al.,Formulation And Evaluation Of Modified Release Oral Hydrogel Beads Of Antidiabetic Drug, world journal of pharmacy and pharmaceutical sciences Volume 3, Issue 3, 2134-2142.
59. BHATT M. B.et.al.,Formulation And Evaluation Of Ionotropically Gelled Novel Hydrogel Beads Of Valsartan, IJPRBS, 2014; Volume 3(2): 845-859.
60. Payal Deepak.et.al.,Pioglitazone Loaded Chitosan Hydrogel Beads: Fabrication And In-

Vitro Characterization, International Journal Of Pharma Professional's Research Volume-7, Issue1, January-2016.

61. J. S. Patil et.al., Ionotropically Gelled Novel Hydrogel Beads: Preparation, Characterization and In vitro Evaluation, Indian J Pharm Sci. 2011 Sep-Oct; 73(5): 504–509.
62. Maiti, Sabyasachi et.al., Sulfated Locust Bean Gum Hydrogel Beads For Immediate Analgesic Effect Of Tramadol Hydrochloride, Journal of Scientific and Industrial Research (JSIR) JSIR Vol.73 [2014].
63. Qing Sheng Zhao et.al., Preparation of alginate coated chitosan hydrogel beads by thermosensitive internal gelation technique, journal of Sol-Gel Science and Technology 54(2):232-237.
64. https://www.drugbank.ca/drugs/DB00491
65. https://gmpua.com/RD/RD/HandbookPharmaceutical%20Excipients.pdf
66. Sejal R Patel,Development and Validation of Analytical Method for Quantitative Estimation of Miglitol and Metformin in Combined Dosage Form. Journal of Applied Pharmaceutical Science 02 (06); 2012: 227-229.
67. P.Trivedi, Verma AM, Garud N."Preparation and characterization of aceclofenac microspheres", Asian J Pharm 2008;4:110-115.
68. Patil JS, Kamlapur MV, Marapur SC, Kadam DV. Ionotropic gelation and polyelectrolyte complexation: The novel technique to design hydrogel particulate sustained, modulated drug delivery system: A review. Digest Journal of Nanomaterials and Biostrectures. 2010; 1: 241-248.
69. Roopa Karki1development and characterization of Valsartan loaded hydrogel beads. Park, H. and K. Park, Biocompatibility Issues of Implantable Drug Delivery Systems. Pharmaceutical Research, 1996. 13(12): p. 1770-1776.
70. K.Kusuma*, M.Nischala, B.Swathi, S.Ramkanth, G.Kusuma.Formulation And Evaluation Of Losartan Hydrogel Beads. Int.J.Pharm Drug Anal Vol: 2 Issue:9 Page:788-795.
71. S.Gibaud, Bonneville D, Astier A. "Preparation of 3,4- diaminopyridine microparticles by solvent- evaporation methods",Int J Pharm 2002;242:197- 201.
72. B.Albertinia, Passerinia N, Sabatinoa MD, Vitali B, Brigidi P, Rodrigueza L. "Polymer– lipid based mucoadhesive microspheres prepared by spray- congealing for the vaginal delivery of econazole nitrate", Eur J Pharm Sci 2009;60:53-62.
73. Pradeesh T, Sunny M, Varma H, Ramesh P. Preparation of microstructured hydroxyapatite microspheres using oil in water emulsions. Indian academy of sciences.2005; 28(5): 383-390.
74. Fundeanu G, Esposito E, Mihai D. Preparation and characterization of alginate Microspheres by a new emulsification method. International Journal of Pharmaceutics. 1998; 170: 11– 21.
75. Desai S, Bolton SA. Floating controlled release drug delivery system. In vitro –In vivo evaluation. Pharm Res. 1993; 10:1321-1325.
76. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52:1145-1149.