FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NATEGLINIDE BY USING NATURAL POLYMERS

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: SATHYASEELAN. V

REG.No.261310264

Under the Guidance of

Dr. R. SAMBATHKUMAR, M.Pharm., PhD,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NATEGLINIDE BY USING NATURAL POLYMERS",** submitted by the student bearing **Reg. No: 261310264** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on……

Internal Examiner **External Examiner**

CERTIFICATE

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Professor & Principal,
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DECLARATON

I do hereby declared that the dissertation **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NATEGLINIDE BY USING NATURAL POLYMERS"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Dr. R. Sambathkumar, M. Pharm., PhD.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **Mr. SATHYASEELAN. V**

Date: **Reg.no. 261310264**

Dedicated to Parents, Teachers & My Family

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SYMBOL INDEX

Symbols		Explanation
Rpm	:	Revolutions per minute
°C	:	Degree celsius
Fig	:	Figure
E.g.	:	Example
Mg	:	Milligram
Min	:	Minutes
Ml	:	Milliliter
µg (mcg)	:	Microgram
µg/ml	:	Microgram per milliliter
%	:	Percentage
SDN	:	Standard deviation
R^2	:	Regression

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1. INTRODUCTION

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improved shelf life of the product. In recent years, considerable attention has been focused on development of sustained release drug delivery systems. The rationale for the development of sustain release drug delivery system of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition.[1]

An ideal drug delivery system should deliver the drug at the rate dictated by the needs of the body over the period of treatment i.e. it should provide the desired therapeutic concentration of drug in the plasma and maintain it constant for the entire duration of treatment.

Sustained release (SR) dosage forms continue to draw attention in the search for improved compliance and decrease the incidence of adverse drug reactions[2]. A sustained release system includes any delivery system that achieves slow release of the drug over an extended period of time.[3]

In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop sustained release dosage forms for many drugs. The primary objective of this system is to ensure safety and to improve efficacy of the drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Pharmacokinetic theory suggests that the ultimate method for reducing the plasma maximum concentration (C_{max}) to plasma minimum concentration (C_{min}) ratio is to have zero- order absorption. Once steady state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists. Successful commercialization of an extended release formulation is usually challenging and involves consideration of many factors such as physiochemical properties of the drug, physiological factors, and manufacturing variables.[1]

The United States Pharmacopoeia (USP) defines the modified-release (MR) dosage form as "the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms"[4]. One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms "controlled release (CR)", "prolonged release", "sustained or slow release (SR)" and "long-acting (LA)" have been used synonymously with "extended release". The commercial branded products in this category are often designated by suffixes such as CR, CD (controlled delivery), ER, LA, PD (programmed or prolonged delivery), Retard, SA (slow-acting), SR, TD (timed delivery), TR (timed release), XL and XR (extended release).

1.1. Advantages and limitations of a sustained release (SR) dosage form

Clinical advantages[5]

- Reduction in frequency of drug administration.
- Improved patient compliance.
- Reduction in drug level fluctuation in blood.
- Reduction in total drug usage when compared with conventional therapy.
- Reduction in drug accumulation with chronic therapy.
- Reduction in drug toxicity (local/systemic).
- Stabilization of medical condition (because of more uniform drug levels).
- Improvement in bioavailability of some drugs because of spatial control.
- Economical to the health care providers and the patient.

1.1.1. Commercial/industrial advantages

- Illustration of innovative/technological leadership.
- Product life-cycle extension.
- Product differentiation.
- Market expansion.
- Patent extension.

1.1.2. Potential limitations

- Delay in onset of drug action.
- Possibility of dose dumping in the case of a poor formulation strategy.
- Increased potential for first pass metabolism.
- Greater dependence on GI residence time of dosage form.
- Possibility of less accurate dose adjustment in some cases.
- Cost per unit dose is higher when compared with conventional doses.
- Not all drugs are suitable for formulating into ER dosage form.

1.2. Criteria for the selection of drug for sustained release dosage form[6] : -

A number of drug characteristics need to be considered in evaluating drug molecules for sustained release dosage form. Some of these characteristics are as follows

Biopharmaceutical Characteristics of the drug:

1.2.1. Dose:

The formulation of sustained release drug products may not be practical for drugs with large conventional dose (>500mg). Because, the size of the SR drug product would have to be quite large for the patient to swallow easily.

1.2.2. Aqueous solubility:

The rate of dissolution is directly proportional to aqueous solubility. Therefore the aqueous solubility of a drug is the limiting factor in its dissolution. In general, too high or too less aqueous solubility of a drug is undesirable for formulation of sustained release dosage form. A drug with very low solubility and slow dissolution rate will exhibit dissolution-limited absorption and yield inherently sustained blood level. High solubility drugs release at faster rates because of their diffusion driving force would be highest are also great challenge for sustain release dosage form.

1.2.3. Partition Coefficient:

Drugs with extremely high partition coefficient readily penetrate the membranes, but are unable to proceed further. While drugs with excessive aqueous solubility i.e. low oil/water partition coefficient cannot penetrate the membrane well. Therefore an ideal drug candidate is one which has a balanced partitioning between oil and water phase.

1.2.4. Drug stability:

Drugs unstable in Gastro-intestinal environment cannot be administered as oral sustained release formulation because of bioavailability problems.

1.2.5. Mechanism and Site of absorption:

Drugs absorbed by carrier-mediated transport process and those absorbed through a window are poor candidates for controlled release system e.g. several B vitamins

1.2.6. Molecular size and Diffusivity:

The lower the molecular weight, the faster and more complete the absorption. In addition to biological membrane the molecule has to diffuse through a polymeric matrix in most of sustained release dosage forms. This diffusion is function of diffusivity of the drug. Diffusivity is defined as the ability of drug to diffuse through the membranes and it is inversely proportional to molecular size.

1.3. Pharmacokinetic Characteristics of the drug:

1.3. 1. Absorption:

For a drug to be administered as controlled release formulation, its absorption rate (Ka) must be efficient since the desired rate – limiting step is rate of drug release Kr. i.e. Kr<<Ka. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug.

1.3.2. Elimination Half Life:

Smaller the $t_{1/2}$, larger the amount of drug to be incorporated in the sustained release dosage form. Drugs with half life in the range of 2 to 8 hours make good candidates for such a system.

1.3. Rate of Metabolism:

A drug, which is extensively metabolized, is suitable for controlled release system as long as the rate of metabolism is not too rapid. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood level would be difficult to maintain.

1.3.4. Dosage form index:

It is defined as the ratio of max steady state conc.($C_{ss.max}$) to min. steady state conc.(C_{ssmin}). Since the goal of sustained release formulation is to improve therapy by

reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible.

1.4. Pharmacodynamic Characteristics of the Drug

1.4.1 Plasma concentration-Response Relationship:-

Drugs whose pharmacological activity is independent of its concentration are poor candidates for sustained release systems.

1.4.2. Therapeutic index:

The release rate of the drug with narrow therapeutic index should be such that the plasma concentration attended is within the therapeutically safe and effective range.

1.5. Various Technologies of sustained release dosage form[3]:

Technologies for designing of sustained release oral dosage forms can be classified according to two characteristics i.e. delivery mechanism and structure of the system. The "Delivery Mechanism" refers to physical and chemical principles involved i.e. dissolution, diffusion, erosion, ion exchange and osmosis. An ideal structure of a controlled release oral dosage form is that which allows the mechanism to yield the desired drug delivery rate.

Depending upon the manner of drug release from the oral sustained release systems, these are classified as,

1. Continuous release systems
2. Delayed release system

1.5.1. Continuous release systems [3]

These systems release the drug for a prolonged period of time along the entire length of gastro- intestinal tract with normal transit of the dosage form. It includes dissolution-controlled release, diffusion-controlled release, ion exchange, pH dependent and osmotic pressure controlled system.

1.5 1.1. Dissolution controlled extended-release systems[3]

A drug with a diminished dissolution rate will provide for extended release, since the liberation of the drug will be limited by the rate of dissolution. The following methods are employed to decrease the dissolution rate of active pharmaceutical ingredients: preparing a salt or derivative of the drug that is less soluble, coating the drug

with a slow dissolving material (encapsulation), or incorporating the drug into a tablet with a slowly dissolving carrier constituent present throughout matrix. The dissolution process can be considered diffusion-layer-controlled, when the rate of diffusion from a solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. Once at steady state, the dissolution process is mathematically described by the Noyes-Whitney equation:

$$\frac{dC}{dt} = K_D \times A \times (C_s - C) = \frac{D}{h} \times A \times (C_s - C) \quad -----(1)$$

Where:

dC/dt = dissolution rate,

A = surface area,

K_D = the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h),

D = diffusion coefficient,

Cs = saturation solubility of the solid,

C = concentration of solute in the bulk solution

Equation (1) predicts that the rate of release will be constant only if the physiochemical characteristics are held constant: surface area, diffusion layer thickness, diffusion coefficient, and concentration difference.

1.5 1.2. Diffusion controlled systems[3]

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer. Two different types of diffusion release systems are categorized: reservoir devices and matrix devices.

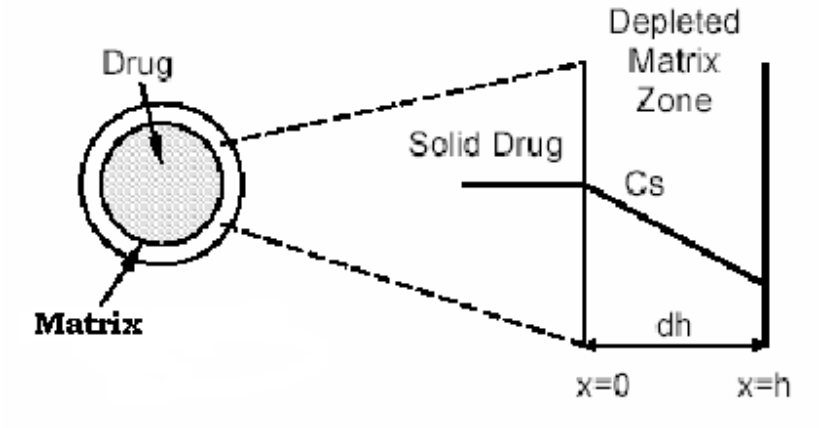
1.5 1. 3. Reservoir Devices:

Extended release formulations where film coating constitutes the main factor in controlled drug delivery. Examples of materials used to control drug release include hardened gelatin, methyl or ethyl cellulose, polyhydroxy methacrylate, methacrylate ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry.

1.5 1. 4. Matrix extended-release systems [3]

In this system, drug in the outside layer exposed to the bathing solution first dissolves and then diffuses out of the matrix. The process continues with the interface between the bulk solution and the undissolved drug moving toward the interior. In order for the system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Release from a monolithic matrix system can be graphically depicted as in fig. 1

Fig.1: Graphic representation of matrix, extended-release system



The release behavior for the system depicted in figure 1 can be mathematically described by the following equation:

$$\frac{dM}{dh} = C_o \times dh - \frac{C_s}{2} \text{---------(2)}$$

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of drug-depleted matrix

C_0 = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix

Drug release from a porous matrix involves the simultaneous penetration of bulk solution into the matrix resulting in the dissolution of drug and exit of the dissolved drug through tortuous interstitial channels and into the bulk solution.

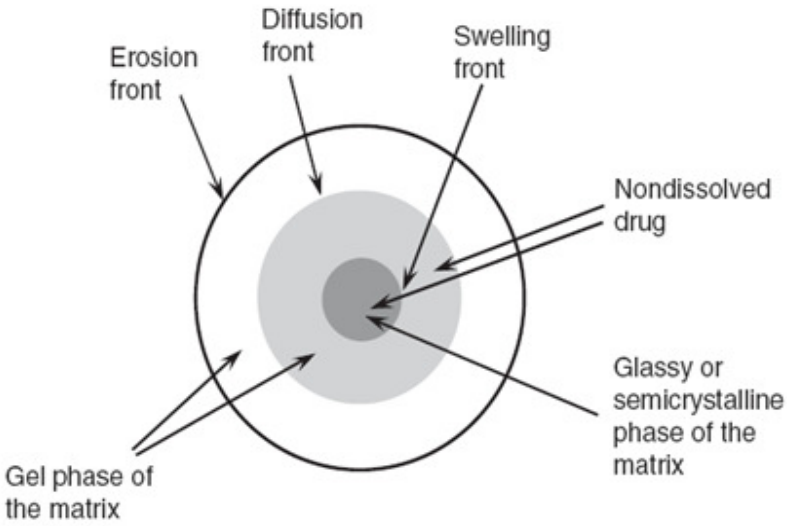
1.5 1. 5. Anomalous release (diffusion and erosion)

In certain systems there is bimodal or anomalous release of the active Pharmaceutical ingredient. In these systems there is diffusion as described previously. Additionally, the extended-release polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusion path length undergoes changes due to polymer dissolution. A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodible matrix[2]. Initially, there are steep water concentration gradients at the polymer/water interface, resulting in water imbibition into the matrix.[6] Due to the imbibition of water, the polymer swells, resulting in dramatic change of drug and polymer concentrations, increasing the dimensions of the system and increasing macromolecular mobility[8.] Upon contact with water the drug dissolves and diffuses out of the device. With increasing water content, the diffusion coefficient of the drug increases substantially[3]. Finally, the polymer itself dissolves.

These systems are described in terms of fronts. The following fronts have been defined, with regard to anomalous release systems: the swelling front, the erosion front, and the diffusion front (Figure 3). The swelling front separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the glass transition temperature (Tg) of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a Tg that is above the respective environmental temperature). The erosion front separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer-concentration-gradient and the well stirred medium[9] .

The diffusion front is between the swelling and erosion front and separates the area of non-dissolved drug from the area of dissolved drug.

Fig. 2: Fronts in an anomalous release system



In 1985, Peppas introduced a semi-empirical equation describing the drug release behavior from anomalous-release (hydrophilic) matrix systems:

$$Q = k \times t^n \text{ ------(3)}$$

Where,

Q = Fraction of drug release in time (t)

t = Time

k = Rate constant (incorporates characteristics of polymer system and drug)

n = Diffusional exponent.

The n value indicates the mechanism of drug release for each particular polymer drug system. For n=0.5, drug release follows a Fickian diffusion mechanism. For n=1, drug release occurs via the relaxation transport that is associated with stresses and phase transition in hydrated polymers. For 0.5<n<1, anomalous release is observed as a result of the contributions from both diffusion and polymer erosion[10]. Perhaps the most comprehensive modeling of a combined diffusion and erosion extended-release system was proposed by Siepmann and Peppas. This model accounts for water and drug concentration-dependent diffusion, in both the radial and axial direction of an extended-release device, and also, accounts for three-dimensional matrix swelling, with subsequent changes in volume, concentration, matrix compositional changes, and simultaneous

polymer dissolution. The model also accounts for drug solubility and non-homogenous swelling through the extended release device.

Other extended/ sustained release systems include:

1.5 1.6. Osmotically controlled systems:

These are reservoir systems into which osmotically active agents are incorporated. The dosage form is coated with a semi permeable membrane. The orifice is made in the membrane layer, often with a laser. Bulk solution diffuses through the membrane and dissolves the osmotic agent(s) creating a high osmotic pressure within the reservoir which will push drug solution out of the orifice. In this type of device, drug release follows zero order kinetics and is pH independent.

1.5 1.7. Ion-exchange systems:

Ion exchange resins are water insoluble, cross-linked polymers that have appended ionic groups along the polymer chain. Drugs are bound to these resins and release depends on the ionic environment and electrolyte concentration of the dissolution medium, as well as on the respective properties of a given ion-exchange resin. Drug is released through an exchange process with an appropriately charged molecule from the dissolution medium exchanging location with the appended drug, followed by diffusion of the drug out of the resin and into the bulk medium.

1.5.2. Delayed release systems:

The design of such system involves release of drug only at a specific site in the gastro intestinal tract. The two types of delayed release systems are intestinal release system and colonic release systems.

1.5.2.1. Intestinal release system:

A drug can be enteric coated for intestinal release for several reasons such as to prevent gastric irritation, prevent destabilization in gastric pH.

1.5.2.2. Colonic release system:

Drugs are poorly absorbed through colon but are delivered to such a site for local action as in the treatment of ulcerative colitis or inflammatory bowel diseases.

1.6. Matrix systems [5]

A matrix tablet is the simplest and the most cost-effective method to fabricate an sustained-release dosage form. The majority of commercially available matrix formulations are in the form of tablets and their manufacture is similar to conventional tablet formulations consisting of granulation, blending, compression and coating steps. In its simplest form, a typical ER matrix formulation consists of a drug, release retardant polymer (hydrophilic or hydrophobic or both), one or more excipients (as filler or binder), flow aid (glidant) and a lubricant.

1.6.1. Advantages:

It is by far the most commonly used Oral CR technology and the popularity of matrix systems can be attributed to several factors.

- Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processing and equipment.
- Development time and cost associated with a matrix system generally are viewed as favorable, and no additional capital investment is required.
- Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level reproducibility, stability of the raw materials and dosage form, and ease of scale-up and process validation.
- In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.
- A matrix system is capable of accommodating both low and high drug load and active ingredients with a wide range of physical and chemical properties.

1.6.2. Limitations:

As with any technology, matrix systems come with certain limitations.

- Matrix systems lack flexibility in adjusting to constantly changing dosage levels, as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected.

- Furthermore, for some products that require unique release profiles (e.g., dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets (e.g., Allegra D) will be required. Nevertheless, we expect continued popularity of matrix systems because they have demonstrated success across a wide range of product profiles.

1.6.3. Types of matrix system[11]:

1.6.3.1. Solid matrix (no disintegration, no swelling)

For the first matrix system, only the drug at the surface is released. The release profile, often expressed as the amount released versus time, is a function of the change of surface geometry and surface area of the matrix. Therefore, the surface geometry and surface area play a significant role in dissolution. In addition, where water-soluble polymers such as polyethylene glycols are used, the viscosity in the diffusion layer adjacent to the dissolution surface also can contribute to the release profile and release rate. If the dissolution/erosion surface and the viscosity in the diffusion layer can be maintained constant during dissolution, a zero-order release profile is obtained. Unless the drug loading is very high (>50 percent), the dissolution rate of the matrix often is determined by the properties of excipients, mainly the solubility and viscosity. The more soluble the excipients and the less viscosity generated in the diffusion layer, the faster is the matrix dissolution. Since only dissolved drug molecules can be absorbed by the body, one should understand the fate of drug solid particles after they are released from the erosion surface of a delivery system. The drug solid particles will start to dissolve in the dissolution medium once they are released.

The dissolution rate of the drug particles is a function of the solubility of the drug and their particle size. For drugs with solubilities 10mg/ml or higher, the dissolution rate of drug particles is usually much faster than the dissolution/erosion rate of matrix systems. Therefore, the release rate of dissolved drug molecules is almost the same as the erosion rate of the matrix. On the other hand, for drugs with solubilities of 0.1 mg/ml or less, the dissolution rate of drug solid particles can be very slow (unless the particles are micronized with particle size less than 10 μm) and is the rate-determining step.

1.6 3.2. Porous matrix (insoluble, no disintegration, no swelling)

For the second type of matrix system, water penetrates the matrix and dissolves the drug particles. This is the only system where use of a polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of a hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides,fatty acids, and polymeric materials such as ethyl cellulose and methacrylate copolymers. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into the formulation. The presence of insoluble ingredients in the formulations helps to maintain the physical dimension of a hydrophobic matrix during drug release. As such, diffusion of the active form from the system is the release mechanism, and the corresponding release characteristic can be described by the Higuchi equation.

Very often, pores form within a hydrophobic matrix as a result of the release of the active ingredient. For a porous monolithic system,

$$Qt = A\sqrt{\frac{\varepsilon}{\tau}\left(2 - \frac{\varepsilon}{\tau}\right) D\varepsilon t} \text{---------- [4]}$$

Where *t* is the tortuosity of the matrix.Tortuosity is introduced to account for an increase in diffusion path length owing to branching and bending of the pores. The square root of time release profile is expected with a porous monolith, whereas the release from such system is proportional to drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drugs because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredients properties or formulation design, incomplete drug release within the gastrointestinal (GI) transit time is a potential risk and needs to be delineated during development [6]. With the growing need for optimization of therapy, matrix systems providing programmable rates of delivery become more important[7].

In this case, both dissolution and diffusion contribute to the release profile according to Eq. (5)

$$\frac{dc}{dt} = D\frac{d^2c}{dx^2} + K(C_s - C) \text{---------- [5]}$$

Where, C = concentration of dissolved drug inside the matrix

Cs = solubility of the drug inside the matrix

D = diffusivity inside the matrix

K = dissolution parameter of the active drug inside the matrix

The first term on the right-hand side of the equation represents diffusion inside a matrix, and the second term corresponds to the particle dissolution. The dissolved drug molecules diffuse out of the matrix and are released into the dissolution medium. At pseudo-steady state (i.e., $dC/dt \approx 0$), the drug concentration inside the matrix will be relatively constant or change slowly with time. This pseudo-steady state concentration inside the matrix will depend on the balance of the dissolution rate of particles and the diffusion rate of dissolved drug substance. If the dissolution rate is much faster than the diffusion rate, the pseudo-steady state concentration inside the matrix will be close to the solubility of the compound. This situation often happens if the solid particles are small or drug loading is high. On the other hand, if solid particles are large and drug loading is low, the pseudo-steady state concentration inside the matrix will be lower than the solubility of the drug substance. Chandrasekaran and Paul have found that for such systems where dissolution is the rate-limiting step, the release is linear with time, and the release rate is a zero order, as shown by

$$\frac{M_t}{M_\infty} = 2\frac{C_0}{C_s}\sqrt{\frac{DK}{l^2}}\left(\frac{1}{2K} + t\right) \text{---------- [6]}$$

where Mt and $M\infty$ = amounts of drug released at time t and infinity

C0 = drug loading

Cs = solubility

D = diffusion constant of drug molecules in the matrix

K = dissolution constant (a function of A/V)

l = thickness of the slab matrix

On the other hand, for systems where diffusion is the rate-limiting step, the release is a function of the square root of time, as indicated by the Higuchi equation.

$$Q_t = \sqrt{C_s\,(2A - C_s)Dt} \text{---------- [7]}$$

At the later stage of drug release, the system is always dissolution controlled because of the low drug loading encountered. Higuchi developed a model to describe the release profile of drug solids dispersed in a matrix. This model ignores the dissolution of drug particles inside a matrix and assumes that the concentration of a drug inside the

matrix is the solubility of the compound. This assumption is only true if a delivery system has high drug loading and is at the early stage of release, where the release is purely diffusion controlled.

Another study also suggested that in dissolution controlled systems (i.e. systems with low drug loading, large drug particle size and at the later stage of dissolution), the drug release from mono dispersed spherical micro particles is a linear function of time, or the release rate is zero order.

1.6.3.3. Water-soluble hydrophilic swellable matrix

The third matrix system is based on hydrophilic polymers that are soluble in water. These are drug delivery systems in which therapeutic agent is dispersed in a compressed matrix made of water swellable polymers which when exposed to aqueous medium , the surface of polymer hydrates to form a viscous gel layer.

The primary rate-controlling ingredients of a hydrophilic matrix are polymers that would swell on contact with the aqueous solution and form a gel layer on the surface of the system. Robust swelling/gelling properties and straightforward manufacturing processes are to a large degree responsible for the versatility and performance of the system. Hydroxypropyl methylcellulose (HPMC) is the most commonly used hydrophilic polymer.

1.7. Dissolution of matrix systems[11]:

The delivery from these systems often follows a certain time course determined by the selection of the polymer and the geometry of the matrix. This type of delivery systems is suitable for reducing the frequency of drug administration, reducing toxicity for drugs with a small therapeutic window, and correcting poor pharmacokinetic behavior such as a short half-life. When solid drug particles are embedded in matrix systems, the release mechanism is more complicated than that of solid-powder systems and largely depends on the design of the matrix systems. There are many types of matrix systems where the release can be expressed using different mathematical models. In this section, only three systems in which dissolution plays a significant role will be discussed.

1.7.1. Surface erodible matrix systems[11]

The first system is a solid matrix that does not disintegrate nor swell during dissolution but dissolves from the surface that is exposed to a dissolution medium. In this case, the drug is released from the eroding surface, and the dissolution profile simply follows Eq. (8) by the Noyes and Whitney equation,

Written as,

$$\frac{dM}{dt} = A \times \frac{D}{h}(C_s - C_b) \quad \text{---------- [8]}$$

Where,

M = mass

t = time

A = dissolving surface area

D = diffusion coefficient

h = thickness of diffusion layer

Cs = solubility

Cb = concentration in bulk solution

1.7.2. Non erodible systems[11]

In the second matrix system, the matrix does not change during dissolution (insoluble, no disintegration, and no swelling). Polymers that are hydrophobic or cross-linked polymers often are used for the matrix. The drug solid is dissolved inside the matrix and is released by diffusing out of the matrix. Both dissolution and diffusion contribute to the release profile of this type of matrix systems. The mathematical expression for this system can be derived from the following equation:

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} + K(C_s - C) \quad \text{---------- [9]}$$

Where,

C = concentration of dissolved drug inside the matrix

Cs = solubility of the drug inside the matrix

D = diffusivity inside the matrix

K = dissolution parameter of the active drug inside the matrix

The first term on the right-hand side of the equation represents diffusion inside a matrix, and the second term corresponds to the particle dissolution.

1.7.3. Soluble matrix systems

The third matrix system is based on hydrophilic polymers that are soluble in water. For these types of matrix systems, water-soluble hydrophilic polymers are mixed with drugs and other excipients and compressed into tablets. On contact with aqueous solutions, water will penetrate toward the inside of the matrix, converting the hydrated polymer from a glassy state (or crystalline phase) to a rubbery state. The hydrated layer will swell and form a gel, and the drug in the gel layer will dissolve and diffuse out of the matrix. At the same time, the polymer matrix also will dissolve by slow disentanglement of the polymer chains. This occurs only for un-cross-linked hydrophilic polymer matrices[13-15]. When such a system is in contact with an aqueous solution, at the early stage of release, the swelling of the matrix causes the erosion front to move outward and the swelling front inward. At the same time, the diffusion front is also receding owing to dissolution of the drug solid in the gel phase and diffusion of the dissolved drug out of the matrix.

During the progress of dissolution, the polymer chains at the erosion front begin to disentangle and dissolve away into the dissolution medium. This surface erosion slows down the swelling (outward movement of the erosion front) and causes the erosion front to recede (inward movement of the erosion front) at the later stages of release.

Their release profile and rate are based on the movements of different fronts (erosion front, diffusion front, and swelling front) during dissolution, as modeled by Eq. (10)

$$\frac{M_t}{M_\infty} = A\sqrt{t} + Bt \quad \text{---------- [10]}$$

where M_t and M_∞ are the amounts of drug released at time t and infinity, and A and B are constants that are functions of the properties of the polymers, drugs, and solvents. The solubility, hydration time, and viscosity of the matrix polymers are the parameters that can be manipulated to change the constants *A* and *B* in Eq. (10) and to modify the release profile and rate of a matrix system. Since the properties of a drug to be delivered (such as solubility and drug loading) are also part of the constants *A* and *B*, selection of a polymer with appropriate properties for a certain desired release profile and

rate should be considered together with the properties of the embedded drug. Selection of polymers with low water solubility, high viscosity, and slow hydration times results in a slow moving erosion front. This makes the constant A in Eq. (10) much larger than constant B, leading to a slow release rate and Fickian release profile. Similarly, for highly water-soluble drugs and low drug loading, the diffusion front can move as fast as the swelling front. The thickness of the gel layer (distance between the erosion front and the swelling front) controls the release of a drug, and the drug release profile follows Fickian behavior. For systems with highly water soluble polymers that hydrate quickly and/or low viscosity, the erosion front moves fast, resulting in a faster drug release rate. In this case, the constant A, in Eq. (10) is much less than B, leading to a linear time release. This situation also can happen for high drug loading systems or not very soluble compounds, where the movement of the diffusion front of these systems may not be as fast as the swelling front. For these systems, the distance between the diffusion and erosion fronts controls drug release instead of the thickness of the whole gel layer (distance between the erosion and swelling fronts). Synchronization of the movement of the diffusion and erosion fronts leads to a zero-order drug release[16,17& 18] . In this case, polymer dissolution is the release controlling factor.

In summary, polymer dissolution (erosion) and diffusion of drug molecules across the gel layer have been identified as the rate-controlling mechanisms. Unlike a pure diffusion-controlled system, the dual release processes make hydrophilic matrices more suitable for insoluble molecules than other diffusion-controlled systems. That is, through formulation design, polymer erosion can be modulated to further aid release control of insoluble compounds[12].

1.8. Hydrophilic matrix system

1.8.1. Classification of hydrophilic polymers[5]:

1. Cellulosic :

   Methyl cellulose

   Hydroxy ethyl cellulose

   Hydroxy propyl methyl cellulose

   Sodium carboxy methyl cellulose etc.

2. Non – cellulosic :

A. Natural gums/Polysaccharides -

Guar gum

Xanthan gum

Karaya gum

Carrageenans

Locust bean gum

Chitosan

Konjac glucomannan etc.

B. Others

Polyethylene oxide

Homopolymers and copolymers of acrylic acid etc.

1. Cellulosic[5]

Chemically, HPMC is mixed-alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropoxyl groups. A general structure of cellulose ether polymers. Type and distribution of the substituent groups affect the physicochemical properties such as rate and extent of hydration, surface activity, biodegradation and mechanical plasticity of the polymer.

2. Polysaccharides[20]

Natural polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Natural gums (like agar in the form of beads and konjac in the form of cylinders) have also been examined as matrices for the sustained release of drugs. When natural gums in the form of compressed tablets are placed in water, they are expected to absorb water from the medium and form a gel before they dissolve in the medium. If a drug is contained in the tablet, it is expected to be released through the gel layer, and sustained release may be achieved. Some natural polymers & their plant source are given below .

Table No. 1. Gums and their sources

Natural gum	Source
Xanthan gum	*Xanthomonas campestris*
Guar gum	Cyamposis tetragonolobus
Carrageenan	Chondrus crispus and Gigartina stellata
Locust bean gum	*Ceratonia siliqua*
Scleroglucan	Sclerotium rolfsii
Gellan gum	Pseudomonas clodea

3. Others[5]:

Polymers of acrylic acid are synthetic high molecular weight polymers that are cross-linked with either allyl sucrose or allyl ethers of pentaerythritol. Because these polymers are cross-linked, they are not water soluble but they swell on hydration and form a gel layer. In case of acrylic acid polymers, surface gel formation is not because of the entanglement of the polymer chains (as the polymers are already cross-linked) but because of the formation of the discrete microgels made up of many polymer particles. Polyethylene oxide (PEO) is also a non-ionic water-soluble resin, available in a variety of molecular weight grades ranging from 100,000 to 7,000,000 Daltons. They are the fastest hydrating water-soluble polymers amongst the hydrophilic polymers, which makes PEO products

A suitable choice for applications where slower initial drug release is required.

1.8.2. Drug Release Mechanism:

1.8.2.1 Glassy to rubbery polymer transition

Swellable matrix drug delivery system must be differentiated from true swelling-controlled delivery systems. True swelling-controlled systems are nonporous matrices in which the drug is essentially immobile when the polymer is glassy (dry), but relatively mobile when the polymer is wet and in the rubbery state. In pharmaceutical practice, swellable matrices are almost exclusively porous dosage forms prepared by compressing a powdered mixture of a drug and a hydrophilic polymer. In the swellable-matrix DDS, which is obtained by compressing discrete drug and polymer particles, drug delivery

could occur even without polymer transition. After a short time, the glassy–rubbery transition of the polymer creates a gel layer that acts as a barrier opposing water and drug transport. An exhaustive treatment of this phenomenon has been given elsewhere[21].

When a matrix that contains a swellable glassy polymer comes in contact with a solvent or swelling agent, there is an abrupt change from the glassy to the rubbery state, which is associated with the swelling process. The individual chains, originally in the unperturbed state[22], absorb water so that their end-to-end distance and radius of gyration expand to a new solvated state. This is because of the lowering of the transition temperature of the polymer (Tg), which is controlled by the characteristic concentration of the swelling agent and depends on temperature and thermodynamic interactions of the polymer–water system. A sharp distinction between the glassy and rubbery regions is observed and the matrix increases in volume because of swelling. On a molecular basis, this phenomenon can activate a convective drug transport, thus increasing the reproducibility of the drug release. The result is an anomalous non-Fickian transport of the drug, owing to the polymer chain relaxation behind the swelling position. This, turn, creates osmotic stresses and convective transport effects[23].

1.8.2.2 The gel layer

Swellable matrices are also termed gel-forming matrices, as their drug-delivery behavior is characterized by the formation of an outer gel layer on the matrix surface, owing to the associated polymer transition. If the polymer gels slowly, the solvent can penetrate deep into the glassy matrix, thus dissolving the drug and disintegrating the matrix. This gel layer acts as a 'protective' layer for the matrix and its stability is as essential as its rapid formation. Therefore, gel-layer thickness behavior is crucial in describing the release kinetics of swellable matrices. The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers do not form the gel layer quickly are not suggested as excipients to be used alone in swellable matrices. However, sometimes they can be used in mixtures with HPMC or other polymers to modulate the swelling behaviour. During drug delivery, the gel layer is exposed to continuous changes in its structure and thickness[23] typically, when the matrix tablet is exposed to an aqueous

solution or gastrointestinal fluids, the surface of the tablet is wetted and the polymer hydrates to form a gelly-like structure around the matrix, which is referred to as the "gel layer". This process is also termed as the glassy to rubbery state transition of the (surface layer) polymer. This leads to relaxation and swelling of the matrix which also contributes to the mechanism of drug release. The core of the tablet remains essentially dry at this stage. In the case of a highly soluble drug, this phenomenon may lead to an initial burst release due to the presence of the drug on the surface of the matrix tablet. The gel layer (rubbery state) grows with time as more water permeates into the core of the matrix, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release[24] . Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, thereby leading to disentanglement and erosion of surface of the matrix. Water continues to penetrate towards the core of the tablet, through the gel layer, until it has been completely eroded. Soluble drugs can be released by a combination of diffusion and erosion mechanisms whereas erosion is the predominant mechanism for insoluble drugs[25].

The gel layer is a hydrophilic barrier that controls water penetration and drug diffusion. It begins when the polymer becomes hydrated and swells. Here, the polymer chains are strongly entangled and the gel layer is highly resistant. However, moving away from this swelling position, the gel layer becomes progressively hydrated and, when sufficient water has accumulated, the chains disentangle and the polymer dissolves[26,27] An interesting analysis of the structure of the gel layer has been performed recently using texture-analysis studies[28] This method offers the advantage of precisely detecting the glassy–rubbery boundary of the matrix. Other methods have been proposed for studying the gel-layer structure using nuclear magnetic resonance[29], ultrasounds[30] or optical techniques[31,32] The concentration at which polymeric chains can be considered disentangled corresponds to an abrupt change in the rheological properties of the gel[33] This value was measured for HPMC polymers and it was not significantly different from the value obtained by fitting drug release data to a model equation that describes gel-layer and drug-release behaviour[34]. A good agreement was shown between the rheological behaviour of HPMC gels and their erosion rate[35]. This confirms that the polymer–

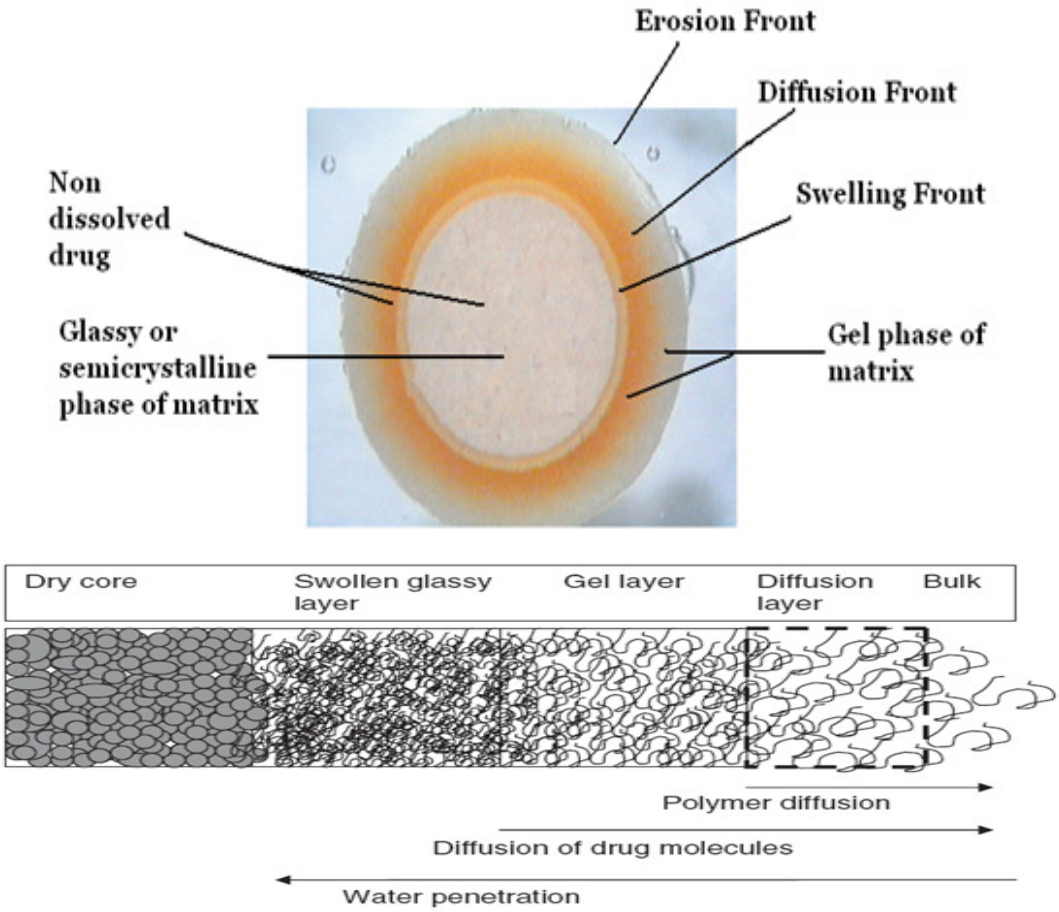
polymer and polymer–solvent interactions are controlling factors for the gel network structure and erosion.

1.8.2.3. Relevant front Description

- The erosion front between the dissolution medium and the erosion (or dissolving) surface.
- The diffusion front between the dissolved and undissolved drug in the gel (or swelled) phase.
- The swelling front between the gel phase and the glassy (or semi crystalline) phase of the matrix.

When such a system is in contact with an aqueous solution, at the early stage of release, the swelling of the matrix causes the erosion front to move outward and the swelling front inward.

Fig.3. Schematic of a swelled hydrophilic polymer matrix showing different fronts



At the same time, the diffusion front is also receding owing to dissolution of the drug solid in the gel phase and diffusion of the dissolved drug out of the matrix. During the progress of dissolution, the polymer chains at the erosion front begin to disentangle and dissolve away into the dissolution medium. This surface erosion slows down the swelling (outward movement of the erosion front) and causes the erosion front to recede (inward movement of the erosion front) at the later stages of release[36].

1.8.2.4. Release Mechanism:

From the previous discussion, it is evident that swellable matrix tablets are activated by water, and drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends on the drug gradient in the gel layer. Therefore, drug concentration and thickness of the gel layer governs the drug flux.Drug concentration in the gel depends on drug loading and solubility. Gel-layer thickness depends on the relative contributions of solvent penetration, chain disentanglement and mass (polymer and drug) transfer in the solvent. At the beginning, solvent penetration is more rapid than chain disentanglement, and a rapid build-up of gel layer thickness occurs. However, when the solvent penetrates slowly, owing to an increase in the diffusional distance, little change in gel thickness is obtained, because penetration and disentanglement rates are similar. Thus, the gel-layer thickness dynamics in swellable matrix tablets exhibit three distinct regimes. The thickness increases when solvent penetration is the fastest mechanism, and remains constant when the disentanglement and water penetration occur at a similar rate. Finally, the gel-layer thickness decreases when the entire polymer has undergone the glassy–rubbery transition[36]. Drug release kinetics are associated with these gel-layer dynamics, ranging initially from Fickian to anomalous (nonFickian), and subsequently from quasi-constant to constant, becoming first-order kinetics in the end. Matrices prepared using swellable polymers of high molecular weight rarely show all of the three regimes during the release time of the drug, because of a low chain disentanglement rate and insufficient external polymeric mass transfer.

In conclusion, the central element of the release mechanism is the gel-layer formation around the matrix in response to water penetration. Phenomena that govern gel-layer formation, and consequently drug-release rate, are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion. Drug release control is

obtained by drug diffusion through the gel layer, which can dissolve or erode. Recently, a convective contribution to drug transport in the gel layer, owing to the extension of polymer chains, was noted. This supports the anomalous behaviour observed in release kinetics[37].

Harland et al. developed a model for drug release based on mass balances of the drug and the solvent at the swelling front and the erosion front**.** The release profile was found to be a combination of Fickian and zero order, as shown by following equation

$$Mt/M\infty = A\sqrt{t} + Bt \text{----------[11]}$$

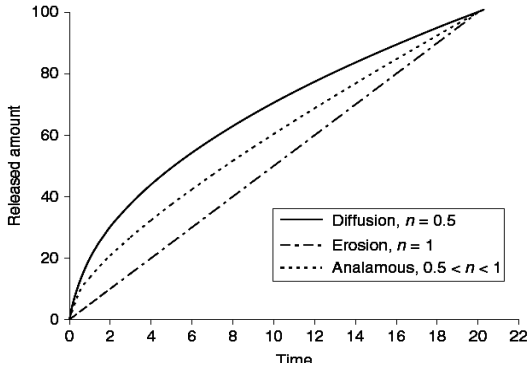
where *Mt* and *M*∞ are the amounts of drug released at time *t* and infinity, and *A* and *B* are constants that are functions of the properties of the polymers, drugs, and solvents. The model suggests that at the early stage of dissolution, the diffusion of dissolved drug molecules through the gel layer limits the dissolution, and the release profile is Fickian.

At the later stage of dissolution, when the erosion front starts to recede, dissolution (or erosion) of the polymer matrix controls the release profile. Therefore, the drug release approaches zero order, especially when the movements of erosion and swelling fronts are synchronized. In general, the release profiles from water-soluble polymer matrix systems often are modeled simply as

$$Mt/M\infty = kt^n \text{ ---------- [12]}$$

Where *k* is the kinetic constant that measures the rate of drug release, and *n* is the release exponent indicative of the release mechanism. If diffusion dominates polymer erosion, the value of *n* would approach 0.5. This often happens at the early stage of release when the polymer matrix is swelling. On the other hand, for erosion-controlled formulations, *n* would approach the value of unity. Under an "anomalous" condition, the value of *n* falls in between 0.5 and 1 when both diffusion and erosion play roles. Figure 4. depicts release profiles under various conditions[38].

Fig.4. Released amount *Qt* versus time *t* plots. Three characteristic drug release profiles from hydrophilic matrices, diffusion, erosional, and anomalous



1.9. Formulation of Hydrophilic Matrices[5]:

Typical formulation of a hydrophilic matrix consists of drug, polymer and excipients. These components can be compressed into tablets directly or after granulation by dry, wet or hot melt method depending on the nature of the drug, excipients and the preference for process in a particular pharmaceutical company. The various formulation and manufacturing considerations in the design of hydrophilic matrices are listed in following table. The development of hydrophilic matrices has largely been empirical. There is no universal recipe/methodology for designing an ER matrix formulation. One can formulate an ER matrix product with different hydrophilic and/or hydrophobic polymers using various manufacturing principles and processes.

A metformin hydrochloride (HCl) extended-release tablet (Glucophage® XR, Bristol Myers Squibb) is a good example of a use of polymer combinations to achieve a desired release profile. The formulation consists of a dual hydrophilic polymer matrix system where the drug is combined with an ionic release-controlling polymer (sodium carboxy methyl cellulose) to form an "inner" phase, which is then incorporated as discrete particles into an "external" phase of a second non- ionic polymer, HPMC[39,40].

There are many other extended-release formulations of metformin HCl approved by US FDA[41]. These formulations range from simple monolithic hydrophilic matrix systems of a single polymer to combination of hydrophilic polymers with or without water-insoluble polymers (including enteric polymers) and hydrophobic matrices[42,43]. Although these formulations vary in their design and compositions, they all achieve similar extended-release profiles when tested in vitro and in vivo (bioequivalent). In the

following sections, some selected fundamental formulation parameters and manufacturing considerations for HPMC matrices are discussed as a general guideline

Key Formulation Considerations:

Table 2: Formulation & manufacturing considerations in the design of hydrophilic matrices for sustained release of drugs

Material/Process	Parameters for considerations
I. Formulation components	
a. Drug	Solubility & permeability, pk_a , dose , stability, particle size
b. Polymer	Particle size, type, level
c. Excipients Filler	 Level/type(solubility)
d. Other excipients 1. Lubricants 2. Others	 Level/type(Stearates, non-stearates & fatty acids/oils) Release rate modifiers, stabilizers, solubilizers, surfactants, buffering agents
II. Manufacturing aspects Manufacturing method	
a. Direct compression	Particle size of polymer/drug, flow aid
b. Dry granulation	Slugging/ roller compaction
c. Wet granulation 1. Solvents 2. Binders 3. Process	 Aqueous/non- aqueous Water-soluble/insoluble, enteric polymers, fatty acids/waxes Low shear High shear Fluidized bed/foamed granulation

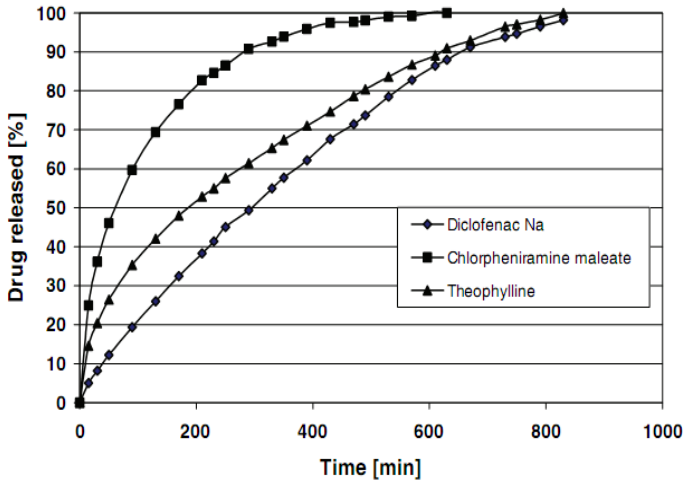
1.9.1. Formulation components

a. Drug Properties

Drug solubility and dose are the most important factors to consider in the design of ER matrices. In general, extended-release formulation of extreme drug solubilities coupled with a high dose is challenging. Drugs with very low solubility (e.g. < 0.01 mg/mL) may dissolve slowly and have slow diffusion through the gel layer of a hydrophilic matrix. Therefore, the main mechanism of release would be through erosion of the surface of the hydrated matrix. In these cases, the control over matrix erosion to achieve consistent extended release throughout the GI tract is critical. For drugs with very high water solubility, the drug dissolves within the gel layer (even with small amounts of

free water) and diffuses out into the media. Therefore, it is important to control the factors that affect drug diffusivity (e.g. pH, gel strength and availability of free water) within the gel layer and parameters that ensure integrity of the gel layer after the drug has been dissolved and released from the gel layer. Drug solubility, therefore, is an important factor determining the mechanism of drug release from HPMC hydrophilic matrices, influencing the choice of polymer viscosity, chemistry and choice of excipients. Use of an appropriate viscosity grade will enable a formulation scientist to design matrices based on diffusion, diffusion and erosion or erosion only mechanisms. For water-soluble drugs, high viscosity grades of HPMC (Methocel K4M CR, K15M CR or K100M CR) tend to generate consistent diffusion controlled systems (n approaching, 0.45) . For drugs with poor water solubility, low viscosity grades HPMC (Methocel K100LV CR and E50LV) are recommended where erosion is the predominant release mechanism (n, 0.9). Depending on drug solubility, it may be necessary to blend polymers of different viscosities to obtain an intermediate viscosity grade of HPMC and achieve desired release kinetics. It should be noted that as drug diffusion is dependent on its molecular weight, chemistry and other excipients within the gel layer, drug release too is dependant on these properties [44].

Fig.5. Influence of drug solubility on their release profiles from a Methocel K4M CR hydrophilic matrix formulation consisting of 30% (w/w) polymer and microcrystalline cellulose as filler



Above figure shows the influence of drug solubility on release profiles for chlorpheniramine maleate, diclofenac sodium and theophylline from a Methocel K4M CR matrix formulation, keeping all other matrix composition and properties constant[45]. As aqueous solubility of the drug is decreased, drug release rate also decreases.

For poorly soluble drugs, particle size of the drug has a major influence on its release profile[46-48]. A decrease in particle size of the drug causes increase in solubility and hence faster drug release rate. Hydrophilic matrix formulation of high-dose drugs (approximating ~1.0 g) is challenging because of the overall dosage weight limitations versus the quantity of the polymer required to achieve desired release profiles. It has been reported that very large tablets that are formulated to be swallowed whole (e.g. ER and delayed release formulations) lead to poor patient compliance and therefore reduced market acceptability[49].

b. Polymer Considerations

Polymer level and viscosity grade are the major drug release controlling factors in HPMC hydrophilic matrices. Depending on dosage size and desired release rate, the typical use level can vary from 20% to 50% (w/w) [50]. For drugs with high water solubility, there is a threshold level of polymer for achieving extended release, and further increase in polymer level may not decrease the drug release rate. However, for obtaining a robust formulation with consistent performance and insensitivity to minor variations in raw materials or manufacturing processes, a usage level of ≥ 30% (w/w) has been recommended[51,52]. Particle size of the polymer is another important factor. The finer the particle size, the faster the rate of hydration of the polymer and hence better the control of drug release[53]. Coarser polymer particles used in a direct compression formulation have been reported to result in faster drug release than finer particles[54]. The coarser the particle size, the slower the hydration rate and gel layer formation. The way to circumvent this problem is the use of fine particle size grades of the polymer. For example, Methocel K Premium CR grades have more than 90% of particles below 149µm or 100mesh. The methoxyl to hydroxypropoxyl substitution ratio of HPMC polymer also influences drug release which generally follows Methocel E (hypromellose 2910) > K (hypromellose 2208).[55] Matrices formulated with high viscosity grades of

HPMC form gel layers with higher gel strengths[56], which results in slower diffusion and erosion rates and hence slower drug release.

c. Presence of Other Excipients

Fillers:

Soluble (e.g. lactose), insoluble (e.g. microcrystalline cellulose, dicalcium phosphate) and/or partially soluble (e.g. partially pregelatinzed starch) fillers are generally used in hydrophilic matrices to enhance pharmacotechnical properties of tablets (improve compressibility, flow and mechanical strength) or to modify the drug release profile. The inclusion of fillers affects the dissolution performance of a matrix by a "dilution effect" on the polymer. The magnitude of the effect on the performance of matrices is dependant on the drug, the polymer level and the level of excipient itself. The presence of water-soluble fillers in high concentrations in the matrix leads to faster and greater water uptake by the matrix, resulting in weaker gel strength, higher erosion of the gel layer and therefore faster drug release. Insoluble but weakly swellable fillers such as microcrystalline cellulose remain within the gel structure and generally result in decreased release rate[57]. The presence of partially pregelatinzed starch such as Starch 1500® in HPMC matrices has been reported to decrease the drug release rate. For a highly soluble or sparingly soluble drug, the rank order of release rate was as follows: lactose > microcrystalline cellulose > partially pregelatinzed starch[58].

d. Others

d.1. Release rate modifiers and stabilizers:

As discussed previously, HPMC is a non-ionic polymer and hence the polymer hydration and gel formation of its matrix is essentially independent of pH of a typical dissolution media used. However, when drugs with pH-dependent aqueous solubility (weak acids or bases) are formulated in HPMC matrices, they may exhibit pH-dependent drug release. Formulating ER matrices of such drugs may lead to lower drug release due to exposure of the dosage form to increasing pH media of the GI tract (from pH 1.2 to 7)[57]. Formulating pH-independent ER matrices for such drugs would not only ensure adequate release throughout the physiological pH, but also lower intra- and inter-patient variability[59,60].

Development of such pH-independent matrices for weakly basic drugs has been shown with the incorporation of acidic excipients (weak acids or salts of strong acids) that lower the micro-environmental pH within the gel layer and thus maintain high local solubility of the drug independent of the external release media[61-67].

Two types of acidic excipients have been used. The first category is "small molecules" or non-polymeric pH modifiers such as adipic, citric, malic, succinic, tartaric, ascorbic or fumaric acid and salts of strong acids such as l-cysteine hydrochloride and glycine hydrochloride. The second category is "large molecules" or polymeric pH modifiers such as sodium alginate, Carbopol and enteric polymers. The extent of micro-environmental control of pH is dependent on the ionization constant and solubility of the release modifier. In general, the higher the pka of the acid, the higher the micro-environmental pH. In addition to control of the micro-environmental pH, the polymeric pH modifiers may also alter the gel strength and erosion rate of the matrix and therefore the release rate of the drug[61,65].

The combination of these two opposing effects could also contribute to pH-independent release profiles. Similar to basic drugs development of pH-independent ER matrices for weakly acidic drugs is possible with incorporation of non-polymeric bases/salts of strong bases and polymeric pH modifiers[68,71]. The examples of basic excipients are sodium, potassium or magnesium salts of bicarbonate, phosphate or hydroxide, magnesium oxide, 2-amino-2-methyl-1, 3-propanediol (AMPD) and Eudragit® E100.The effectiveness of this approach often depends on the properties of the drug and the release-modifying agent as well as the ratio of the drug to release-modifying excipient. In matrix systems, a small molecule pH modifier (such as tartaric acid or citric acid) that is water soluble can leach out of viscous gel layer fairly quickly, resulting in a limited change of pH in the gel layer over an extended duration of the drug release. Thus, it is important to design a system that retains the release modifying agent in a delivery device suitable for the extended period of release. Polymeric pH modifiers are a better choice in such situations as they have higher molecular weights and provide longer residence times in the matrix. However, the magnitude of pH modulation provided by the polymeric pH modifiers is not expected to be comparable to that provided by non-polymeric acids, and in some cases it might be necessary to include an additional "small

molecule" pH modifier in the matrix formulation. pH modifiers are also used for improving the stability of active pharmaceutical ingredients in the matrix composition. Bupropion hydrochloride, for example, is an antidepressant drug that undergoes degradation in an alkaline environment. To formulate an acceptable ER solid dosage form, the use of weak acids or salts of strong acids as stabilizers in the formulation (tartaric acid, citric acid, ascorbic acid, l-cysteine hydrochloride and glycine hydrochloride) has been suggested in the literature. These stabilizers provide an acidic environment surrounding the active drug that prevents its decomposition[72].

d.2. Effect of Salts and Electrolytes :

In general, as the concentration of ions in a polymer solution increases, polymer hydration or solubility decreases[73]. The amount of water available to hydrate the polymer is reduced because more water molecules are required to keep the ions in solution. Moreover, the types of ions in solution affect polymer hydration to varying degrees. The susceptibility of cellulose ethers to ionic effects follows the lyotropic series of the ions (chloride < tartarate < phosphates and potassium < sodium)[74]. Changes in the hydration state of a polymer in solution are manifested primarily by changes in solution viscosity and turbidity or cloud point. At low ionic strengths, the polymer hydration is unaffected, but higher ionic strengths may lead to a loss of gel integrity of the matrix. The extent of this influence depends on the polymer type and lyotropic series of the ions. The effect of electrolytes or salts is important only in cases where high concentrations of salts or electrolytes are present as tablet components or as constituents of dissolution media. In-vivo conditions, however, have fairly low ionic strength (ionic strength of gastrointestinal fluids, μ = 0.01–0.15) to affect the polymer hydration and have significant impact on release rate[75].

1.9.2 Method of Manufacture

Hydrophilic matrix tablets are manufactured using traditional tablet manufacturing methods of direct compression (DC), wet granulation or dry granulation (roller compaction or slugging) depending on formulation properties or on manufacturer's preference. HPMC polymers generally have very good compressibility and results in tablets with high mechanical strength[76]. It has been reported that high

molecular weight grades of HPMC may undergo less plastic flow than the low molecular weight grades and thus require higher pressures to deform[77]. In a matrix formulation, the inclusion of DC excipients and other ingredients may render the formulation for direct compressionwith acceptable mechanical properties of the tablets.

Aqueous wet granulation is generally achieved using a spray system to avoid formation of a lumpy mass[78]. Addition of a binder may not be necessary as HPMC itself has excellent binder properties when hydrated. Over-granulation or high concentration of a binder beyond the optimal level could adversely affect the compressibility of the granules. To reduce the formation of a lumpy mass during granulation and improve process efficiency, a novel foam granulation technology has recently been introduced[79]. In this method, using a simple foam apparatus, air is incorporated into a solution of conventional water-soluble polymeric binder such as a low viscosity grade HPMC to generate foam. Application of such foam for granulation results in an increased surface area and volume of polymeric binder and therefore improves the distribution of water/binder system throughout the powder bed. The effect of compression force on drug release from hydrophilic matrices is minimal when tablets are made with sufficient strength and optimum levels of polymers are used[80]. One could relate variation in compression forces to a change in the porosity of the tablets. However, as the porosity of the hydrated matrix is independent of the initial porosity, the compression force is expected to have little influence on drug release rate[81]. Once sufficient tablet hardness suitable for processing and handling is achieved, tablet hardness would have little further effect on drug release profile. To ensure consistent porosity and avoid entrapment of air within the dry tablet core, a pre-compression step may have to be considered in the manufacture of matrices. Compression speed has been reported to adversely affect the tensile strength of the tablets and lower compression speed has been suggested for obtaining a product with better mechanical quality[82-84]. A robust formulation, which is insensitive to changes in the manufacturing processes such as over-granulation effect or variable tablet hardness, may be obtained by reducing the amount of intragranular HPMC and replacing it as an extra granular component[85].

1.9.3. Viscous Synergism between polymers

It is known than the blending of certain types of gums can produce a disperse system with a greater viscosity than the sum of the viscosities of the individual gum dispersions considered separately. This phenomenon is called viscous synergism[86]. In this sense, viscous synergism has been investigated between guar gum, locust bean gum, xanthan gum, carrageenans (k & λ)etc., and starch or other hydrocolloids based on the comparison of the corresponding flow curves[87-91]. In turn, analyses of the rheological properties of these preparations have contributed to further knowledge of the interaction between carrageenans and galactomannans[92-96]. Viscous synergism index," *I*, defined as:

$$I_v = \frac{n_{i+j}}{n_i + n_j} \quad \text{---------- [13]}$$

where i and j represent the two gums forming the mixed system, i+j. The aqueous dispersions of the systems i, j and i+j must be formulated at the same total concentration. It is clear that the index defined by Equation (13) always presents positive values. However, in the study of synergism, different intervals can be considered. If *I* is between 0 and 0.5, the viscosity of the mixed system will be less than the sum of the viscosities of its two constituent simple systems, and also less than at least one of them—thus showing inter-action between the two gums to be antagonistic. If Equation (13) was used in application to a single system itself, or to two systems of equal viscosity in the absence of interactions between them, then, $n_i = n_j = n_{i+j}$ and thus the synergism index would be Iv = 0.5(i.e., indicating the lack of interaction). On the other hand, for an Iv value of between 0.5 and 1.0, where in addition the two conditions, $n_{i+j} > n_i$ and $n_{i+j} > n_j$ apply, synergistic effects will occur. However, if either of the above two conditions are not met, the effect of mixing both gums lacks practical interest in terms of viscous synergism, since one of the two simple systems would in itself prove more viscous than the mixed system. Lastly, when $Iv > 1$, the viscosity of the mixed system, would be greater than the sum of the viscosities of the two simple systems, i.e. synergism would result[90].

2. LITERATURE REVIEW

1. **Andreopoulos *et al.,*** 2001 studied the use of xanthan gum as a carrier for controlled drug delivery. They prepared systems based on xanthan gum matrix containing 1%, 2% and 5% salicylic acid was prepared and studied as controlled release devices & found that swelling behaviour of xanthan gum is useful in predicting the drug release from matrix.[97]
2. **Sankalia *et al.,*** 2008 studied the effect of polymeric blends of ethyl cellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, xanthan gum, guar gum , Starch 1500, and lactose on in vitro release profiles were studied and fitted to various release kinetics models and examine a level A in vitro – in vivo correlation (IVIVC) for glipizide hydrophilic sustained release matrices. They found that direct compression of drug release retardant xanthan gum with other rate controlling excipients effectively controls glipizide release throughout the course of 12 h[98].
3. **Varshosaz *et a.l***,2006 developed matrix sustained release tablets of highly water-soluble tramadol HCl using xanthan gum and guar gum and compared with the extensively investigated hydrophilic matrices i.e. hydroxypropylmethylcellulose, carboxymethylcellulose with respect to in vitro drug release rate and hydration rate of the polymers. They found that xanthan gum has a higher drug retarding ability than guar gum & no synergistic effect was seen for mixtures of gums with HPMC.[99]
4. **Khullar *et al.,*** 1998 studied guar gum as a matrix former for sustained release tablets and examined mechanism of behaviour of guar gum in a polymer drug matrix and found that swelling behaviour of guar gum is useful in predicting the drug release from matrix[100].
5. **Fassihi *et al.***, 2001 investigated the effect of ionic and non-ionic excipients and additives as modulators of swelling and erosion kinetics and verapamil HCl release from guar-based matrix tablets. They found that ionic, water soluble materials (sodium chloride, glycine) reduce initial hydration of the matrix and thus have the ability to limit the initial rapid diffusion of drug and to sustain near linear release over 24 h[101].
6. **Jun *et al.,*** 2005 investigated the effects of carrageenans (iota & lambda) and cellulose ethers (HPMC & MC) on the drug release rates of ibuprofen controlled-

release tablet matrices prepared by direct compression. They found that both lambda and iota carrageenan can be used in combination with cellulose ethers for the formulation of controlled-release ibuprofen tablets[102].

7. **Hernandez *et al.*,** 2001 studied the synergistic interactions between locust bean gum (LBG) and two types of carrageenans (k and λ). They found that the highest synergism corresponded to the lowest proportion of k and λ carrageenan.[103]
8. **Bonferoni *et al.,*** 1993compared λ carrageenan with sodiumcarboxymethylcellulose and xanthan gum. They found that it controls the initial burst release and drug release is independent of pH of the dissolution of the medium[104].
9. **Bonferoni *et al.*,** 1994 studied the suitability of λ-carrageenan-hydroxypropylmethylcellulose (HPMC) matrices for the controlled release of two basic drugs (salbutamol sulphate and chlorpheniramine maleate). They found that λ -carrageenan hydrophilic matrices for sustained release of soluble basic drugs and the addition of HPMC can reduce the impact of the medium characteristics on the attrition behaviour of the matrix[105].
10. **Pellicer *et al.*,** 2000 studied an empirical approach to quantify the synergistic interactions & their variations with shear rate and the influence of addition of third gum NaCMC. They found that viscosity of xanthan gum and locust bean gum was three fold greater than that of xanthan gum, locust bean gum and NaCMC[106].
11. **Pricl *et al.,*** 1997 studied the synergistic gelation of xanthan gum with locust bean gum. They found that the highest synergistic effect is attained for the locust bean gum and xanthan gum 1:1 system[107].
12. **Venkataraju *et al.,*** 2007 developed a controlled drug delivery of highly water soluble drug, propranolol hydrochloride using synergistic activity of locust bean gum and xanthan gum. They found that the XLBG matrices offer more precise results than X and LBG matrices due to the effect of a synergistic interaction between the two biopolymers[108].
13. **Parakh *et al.,*** 2003 studied the novel method to study the water absorption rate for swellable matrices and predicting the role of water absorption rate in drug release pattern. They found that rate of water absorption depends on the ratio of polymer: hydrophilic excipient and polymer viscosity[109].

14. **Kinget *et al.,*** 1994 studied the swelling and drug release behaviour of xanthan gum matrix tablets using three drugs having different properties, i.e., caffeine as a soluble neutral drug, indomethacin as an insoluble acidic drug, and the sodium salt of indomethacin as a soluble acidic drug. They established the dependence of drug release on the swelling of the polymer matrix and on the type of the drugs[110].
15. **Munday *et al.,*** 2000 studied xanthan gum and Karaya gum as release controlling agent. They found that both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role[111].
16. **Munday *et al.,*** 1997 studied the swelling, erosion and solvent front penetration properties of mini-matrices containing xanthan (X), locust bean (LB) and karaya (K) gums were examined, analysed and related to the overall in vitro release kinetics of diclofenac sodium. They found that the dominant mechanism fickian drug diffusion and polymer erosion depended on the nature and content of the gum, as well as the stage in the dissolution time period[112].

3. AIM AND OBJECTIVES

AIM :

Recently, sustained release drug delivery system has become the standards in the modern pharmaceutical design and intensive search has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral sustain release medication will continue to account for the largest share of drug delivery systems, due to ease of its formulation as compared to other systems. The biggest ascent of these type of systems is the ease with which they can be prepared on the large scale, and hence, easy commercialization.

For treating diabetes, it has been considered important that both a post prandial blood glucose level and a fasting blood glucose level are decreased to make them to normal levels. Other antidiabetics are primarily used for decreasing either a post prandial blood glucose level or a fasting blood glucose level to make it close to a normal level, but nateglinide has been used to control both post prandial blood glucose level as well as a fasting blood glucose level. Nateglinide is a BCS class II (Insoluble, highly permeable) drug. The plasma half life of nateglinide is 1.5h. The usual oral dosage regimen is 60—180mg taken 3 times a day for nateglinide immediate release tablets. The nateglinide controlled or sustained release formulation would be more useful than the nateglinide immediate release tablets from the view point of avoidance of side effect, or of easy control of both PBG and FBG to enable control of both PBG and FBG for moderate and severe diabetes patients. Thus, there is a need to formulate oral sustained drug delivery system of nateglinide.

The oral sustained release drug delivery system of nateglinide can be formulated using various synthetic as well as natural hydrophilic polymers. The biodegradable nature and easy availability of the natural polymers makes them suitable for using as a sustained release polymer. The natural polymers also exhibit a rheological synergism between them when two polymers are mixed together. By using this property of the natural polymers can be used to reduce the total polymer concentration from the sustained release matrix tablet and once a day formulation of the nateglinide can be formulated containing least amount of polymer.

Nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] is a novel mealtime glucose regulator approved for the treatment of type II diabetes mellitus. Nateglinide has a rapid onset and short duration of insulinotropic action that results in reduction of mealtime glucose rise and lowers the postabsorptive potential for hypoglycemia in humans and experimental animals.

OBJECTIVE:

1. To prepare and evaluate once a day sustained release matrix tablet of Nateglinide.
2. To reduce the total polymer concentration using rheological synergism between two natural gums.
3. To study the *invitro* performance of matrix tablet.

4. PLAN OF WORK

1. Literature review
2. Selection of suitable drug and excipients
3. Procurement of drug and excipients
4. Characterization of drug
5. Preformulation studies
6. Preliminary studies
7. Evaluation of granules
8. Formulation and development of hydrophilic matrix tablet
9. Evaluation of matrix tablets
10. In vivo performance of matrix tablet
11. Stability studies of matrix tablet

5. DISEASE PROFILE [14,15]

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of Polyuria(frequent urination), Polydipsia(increased thirst) and Polyphagia(increased hunger)[27].

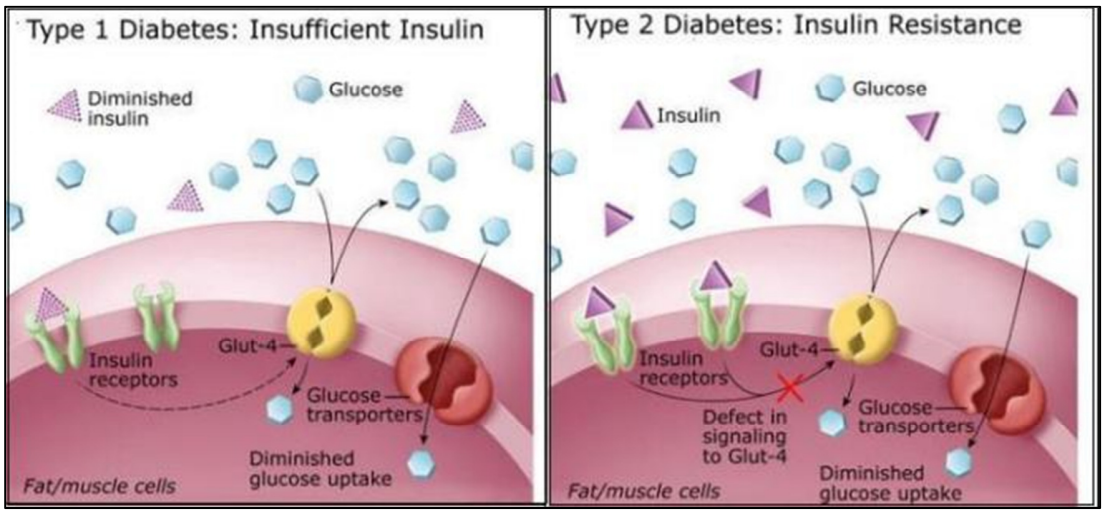
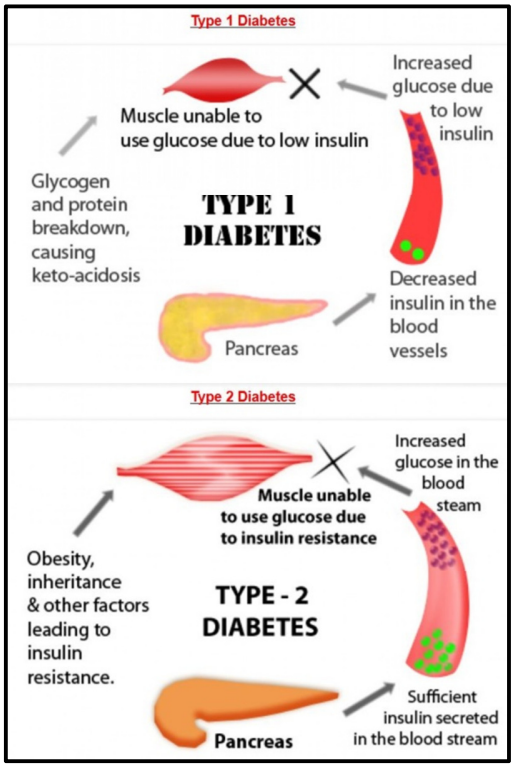


Fig.No.6 & 6a: Comparison of Type-I & Type-II Diabetes mellitus

The three main types of diabetes mellitus (DM) are:

- Type 1 DM results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as insulin-dependent diabetes mellitus (IDDM) or "juvenile" diabetes)
- Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as noninsulin-dependent diabetes mellitus (NIDDM) or "adult-onset" diabetes)



- Gestational diabetes is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Both types 1 and 2 are chronic conditions that usually cannot be cured.

Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass surgery has been successful in many with morbid obesity and type 2 DM. Gestational diabetes usually resolves after delivery.

Diabetes without proper treatments can cause many complications. Acute complications include Hypoglycemia, Diabetic Ketoacidosis, or Nonketotic Hyperosmolar Coma.

Serious long-term complications include Cardiovascular Disease, Chronic Renal Failure, and Diabetic Retinopathy (retinal damage).

Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

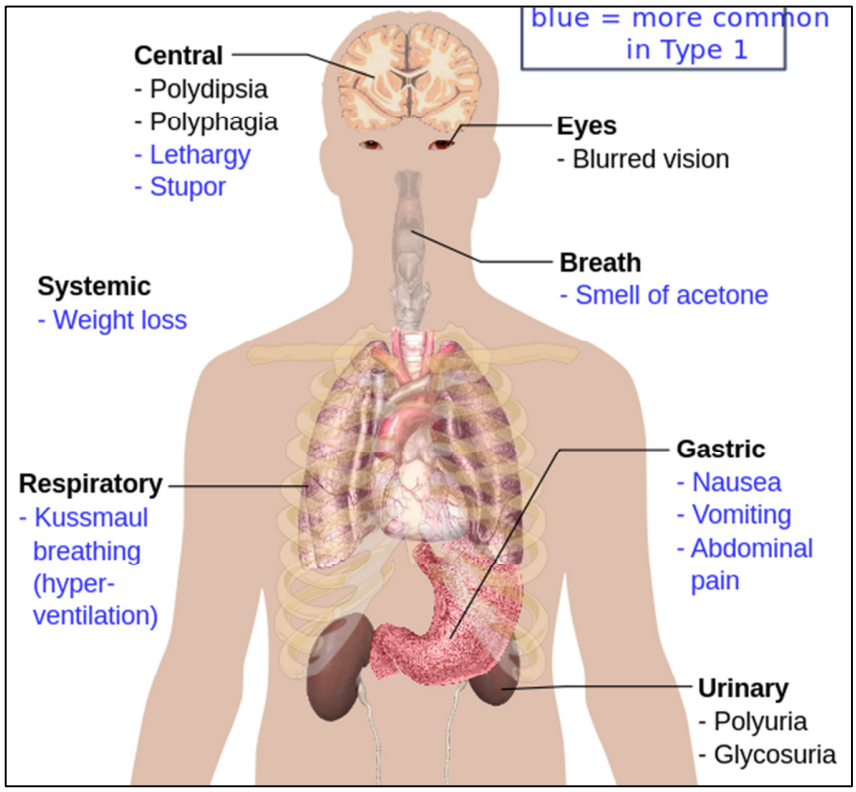
Signs and symptoms:

The classical symptoms of untreated diabetes are loss of weight, Polyuria(frequent urination), Polydipsia(increased thirst) and Polyphagia(increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes [28].

Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas with type 2 changes are generally more gradual,

but should still be suspected. A number of skin rashes that can occur in diabetes are collectively known as Diabetic Dermadromes.

Fig.No.7 : Overview of the most significant symptoms of diabetes.



Diabetic emergencies:

People (usually with type 1 diabetes) may also present with diabetic ketoacidosis, a state of metabolic dysregulation characterized by the smell of acetone, a rapid, deep breathing known as Kussmaul breathing, nausea, vomiting and abdominal pain, and altered states of consciousness.

A rare but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration.

Complications

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease.

The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease.

Diabetes also causes "micro vascular" complications—damage to the small blood vessels. Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to visual symptoms, reduced vision, and potentially blindness. Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.

Causes:

The cause of diabetes depends on the type.

Type 1 diabetes is partly inherited, and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. A genetic element in individual susceptibility to some of these triggers has been traced to particular HLAgenotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 DM seems to require an environmental trigger [29].

Type 2 diabetes is due primarily to lifestyle factors and genetics.

The following is a comprehensive list of other causes of diabetes:

Table. No. 3: causes of diabetes

• Genetic defects of β-cell function
  o Maturity onset diabetes of the young
  o Mitochondrial DNA mutations
• Genetic defects in insulin processing or insulin action
  o Defects in proinsulin conversion
  o Insulin gene mutations
  o Insulin receptor mutations
• Exocrine pancreatic defects
  o Chronic pancreatitis
  o Pancreatectomy
  o Pancreatic neoplasia
  o Cystic fibrosis
  o Hemochromatosis
  o Fibrocalculous pancreatopathy
	• Endocrinopathies
	  o Growth hormone excess (acromegaly)
	  o Cushing syndrome
	  o Hyperthyroidism
	  o Pheochromocytoma
	  o Glucagonoma
	• Infections
	  o Cytomegalovirus infection
	  o Coxsackievirus B
	• Drugs
	  o Glucocorticoids
	  o Thyroid hormone
	  o β-adrenergic agonists
	  o Statins[17]

Diagnosis:

Table No. 4: Diabetes diagnostic criteria

Condition	**2 hour glucose**	**Fasting glucose**	**HbA_{1c}**
	mmol/l(mg/dl)	**mmol/l(mg/dl)**	**%**
Normal	<7.8 (<140)	<6.1 (<110)	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) &<7.0(<126)	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥6.5

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)
- Plasma glucose ≥ 11.1 mmol/l (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (Hb A1C) ≥ 6.5%

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) are considered diagnostic for diabetes mellitus [30].

People with fasting glucose levels from 110 to 125 mg/dl (6.1 to 6.9 mmol/l) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease.

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

Medications

Oral medications

Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality. Routine use of aspirin, however, has not been found to improve outcomes in uncomplicated diabetes.

Insulin

Type 1 diabetes is typically treated with combinations of regular and NPH insulin, or synthetic insulin analogs. When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications.[29] Doses of insulin are then increased to effect.

Epidemiology

Globally, as of 2010, an estimated 285 million people had diabetes, with type 2 making up about 90% of the cases. Its incidence is increasing rapidly, and by 2030, this number is estimated to almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030. The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented.

Australia

Indigenous populations in first world countries have a higher prevalence and increasing incidence of diabetes than their corresponding non-indigenous populations. In Australia, the age-standardized prevalence of self-reported diabetes in indigenous Australians is almost four times that of non indigenous Australians. Preventative community health programs, such as Sugar Man (diabetes education),are showing some success in tackling this problem.

China

Almost one Chinese adult in ten has diabetes. A 2010 study estimated that more than 92 million Chinese adults have the disease, with another 150 million showing early symptoms. The incidence of the disease is increasing rapidly; a 2009 study found a 30% increase in 7 years.

India

India has more diabetics than any other country in the world, according to the International Diabetes Foundation, although more recent data suggest that China has even

more. The disease affects more than 50 million Indians - 7.1% of the nation's adults - and kills about 1 million Indians a year. The average age on onset is 42.5 years. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class.

United Kingdom

About 3.8 million people in the United Kingdom have diabetes mellitus, but the charity Diabetes U.K. has made predictions that that could become high as 6.2 million by 2035/2036. Diabetes U.K. have also predicted that the National Health Service could be spending as much as 16.9 billion pounds on diabetes mellitus by 2035, a figure that means that the National Health Service could be spending as much as 17% of its budget on diabetes treatment by 2035.

United States

For at least 20 years, diabetes rates in North America have been increasing substantially. In 2010, nearly 26 million people have diabetes in the United States, of whom 7 million people remain undiagnosed. Another 57 million people are estimated to have prediabetes.

The Centers for Disease Control and Prevention (CDC) has termed the change an epidemic. The National Diabetes Information Clearinghouse estimates diabetes costs $132 billion in the United States alone every year. About 5%–10% of diabetes cases in North America are type 1, with the rest being type 2. The fraction of type 1 in other parts of the world differs. Most of this difference is not currently understood. The American Diabetes Association (ADA) cites the 2003 assessment of the National Center for Chronic Disease Prevention and Health Promotion (Centers for Disease Control and Prevention) that one in three Americans born after 2000 will develop diabetes in their lifetimes.

According to the ADA, about 18.3% (8.6 million) of Americans age 60 and older have diabetes. Diabetes mellitus prevalence increases with age, and the numbers of older persons with diabetes are expected to grow as the elderly population increases in number. The National Health and Nutrition Examination Survey (NHANES III) demonstrated, in the population over 65 years old, 18% to 20% have diabetes, with 40% having either diabetes or its precursor form of impaired glucose tolerance.

Treatment

Treatment goals for type 2 diabetic patients are related to effective control of blood glucose, blood pressure and lipids to minimize the risk of long-term consequences associated with diabetes. They are suggested in clinical practice guidelines released by various national and international diabetes agencies.

- Blood sugar control — the goal of treatment in type 2 diabetes is to keep blood sugar levels at normal or near-normal levels. Careful control of blood sugars can help prevent the long-term effects of poorly controlled blood sugar (diabetic complications of the eye, kidney, and cardiovascular system).
- Home blood sugar testing — in people with type 2 diabetes, home blood sugar testing is often recommended.
- Cardiovascular risk control — the most common long-term complication of type 2 diabetes is cardiovascular (heart) disease, which can cause myocardial infarction (heart attack), angina (chest pain), stroke, and even death. The risk of heart disease is estimated to be at least twice that of persons without diabetes.

Classification of Antidiabetic agent

1. Insulin
2. Oral antidiabetic drugs
   a) Sulfonylureas
      I. First-generation agents
         Tolbutamide , Acetohexamide, Tolazamide, Chlorpropamide
      II. Second-generation agents
         Glipizide, Glyburide, Glimepiride, Gliclazide
   b) Meglitinides
      Repaglinide, **Nateglinide**
   c) Biguanides
      Metformin, Phenformin, Buformin
   d) Thiazolidinediones
      Rosiglitazone, Pioglitazone, Troglitazone
   e) Alpha-glucosidase inhibitors

6. DRUG PROFILE [15,16,17,18.19]

1. Category: Ant diabetic Agent

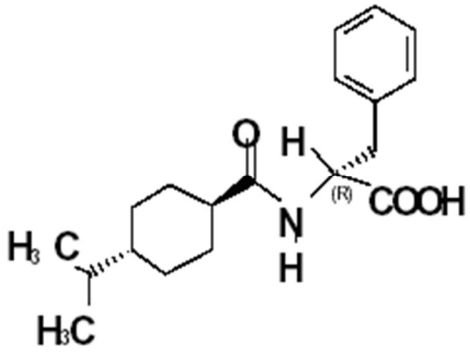


Fig.8. Structure of Nateglinide

2. Molecular Formula: $C_{19}H_{27}NO_3$

3. Molecular weight: 317.43

4. Chemical Name: Nateglinide is N-(trans-4-Isopropylcyclohexanecarbonyl)-D-phenylalanine.

5. Description :

Nateglinide is amorphous white powder.

6. Melting Range: 133 – 139^0C

7. Dissociation constant: 3.1

8. Solubility: It is freely soluble in methanol, ethanol, and chloroform, soluble in ether, sparingly soluble in acetonitrile and octanol, and practically insoluble in water.

9. Pharmacokinetics of Nateglinide:

9.1 Half life: 1.5 hr.

9.2. Absorption

Following oral administration immediately prior to a meal, nateglinide is rapidly absorbed with mean peak plasma drug concentrations (C_{max}) generally occurring within 1

hour (Tmax) after dosing. When administered to patients with Type 2 diabetes over the dosage range 60 to 240 mg three times a day for one week, nateglinide demonstrated linear pharmacokinetics for both AUC (area under the time/plasma concentration curve) and C_{max}. T_{max} was also found to be independent of dose in this patient population. Absolute bioavailability is estimated to be approximately 73%. When given with or after meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in C_{max} and a delay in time to peak plasma concentration (T_{max}). Plasma profiles are characterized by multiple plasma concentration peaks when nateglinide is administered under fasting conditions. This effect is diminished when nateglinide is taken prior to a meal.

9.3. Distribution

Based on data following intravenous (IV) administration of nateglinide, the steady state volume of distribution of nateglinide is estimated to be approximately 10 liters in healthy subjects. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent 1 acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 µg/mL.

9.4. Metabolism

Nateglinide is metabolized by the mixed-function oxidase system prior to elimination. The major routes of metabolism are hydroxylation followed by glucuronide conjugation. The major metabolites are less potent antidiabetic agents than nateglinide. The isoprene minor metabolite possesses potency similar to that of the parent compound nateglinide. In vitro data demonstrate that nateglinide is predominantly metabolized by cytochrome P450 isoenzymes CYP2C9 (70%) andCYP3A4 (30%).

9.5. Excretion

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% of the administered $_{14}C$ nateglinide was recovered in the urine. Eighty-three percent of the $_{14}C$-nateglinide was excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the $_{14}C$-nateglinide was excreted in the urine as parent compound. In all studies of

healthy volunteers and patients with Type 2 diabetes, nateglinide plasma concentrations declined rapidly with an average elimination half-life of approximately 1.5 hours. Consistent with this short elimination half-life, there was no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days.

10. Mechanism of Action:

Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium (K+ATP) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue selective with low affinity for heart and skeletal muscle.

11. Adverse effects:

Very rarely hypoglycemia

12. Dose:

Initial dose: 120 mg orally 3 times a day before meals

Maintenance dose: 60 to 120 mg orally 3 times a day before meals

7. EXCIPIENTS PROFILE

Carrageenan

1. Nonproprietary Names

   USP NF: Carrageenan

2. Synonyms

Chondrus extract, E407, Gelcarin, Genu, Hygum TP-1, Irish moss extract, Marine Colloids, SeaSpen PF, Viscarin.

3. Chemical Name

Carrageenan, κ-Carrageenan, λ-Carrageenan

4. Empirical Formula and Molecular Weight

The USPNF 23 describes carrageenan as the hydrocolloid obtained by extraction with water or aqueous alkali from some members of the class Rhodophyceae (red seaweed). It consists chiefly of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3, 6-anhydrogalactose copolymers. These hexoses are alternately linked at the α-1, 3 and β-1, 4 sites in the polymer.

5. Structural Formula

The carrageenans are divided into three families according to the position of sulfate groups and the presence or absence of anhydro galactose.

λ-Carrageenan (lambda-carrageenan) is a non gelling polymer containing about 35% ester sulfate by weight and no 3,6-anhydrogalactose.

ι-Carrageenan (iota-carrageenan) is a gelling polymer containing about 32% ester sulfate by weight and approximately 30% of 3,6-anhydrogalactose.

κ-Carrageenan (kappa-carrageenan) is a strongly gelling polymer which has a helical tertiary structure that allows gelling. It contains 25% of ester sulfate by weight and approximately 34% of 3, 6-anhydrogalactose.

6. Functional Category

Emulsifying agent, gel base, stabilizing agent, suspending agent, sustained release tablet matrix, viscosity-increasing agent**.**

7. Typical Properties

Because of the vast differences in the material that can be referred to as carrageenan, it is difficult to give descriptions of typical properties

Table No. 5: Typical properties of carrageenans

Trade name	Carrageenan type	Gel type	Solubility in water	Viscosity	Use concentration (%)	Use examples
Gelcarin GP-379	Iota	Elastic, medium strength	Hot	High, thixotropic	0.3–1.0	Creams, suspensions
Gelcarin GP-812	Kappa	Brittle, strong	Hot	Low	0.3–1.0	Gels
Gelcarin GP-911	Kappa	Brittle, firm	Hot, partial in cold	Low	0.25–2.0	Encapsulation
SeaSpen PF	Iota	Elastic, weak	Cold, delayed gel formation	Medium, thixotropic	0.5–1.0	Creams, suspensions, lotions
Viscarin GP-109	Lambda	Non-gelling	Partial cold, full in hot	Medium	0.1–1.0	Creams, lotions
Viscarin GP-209	Lambda	Non-gelling	Partial cold, full in hot	High	0.1–1.0	Creams, lotions
Viscarin GP-328	Kappa /lambda	Weak	Hot	Medium –high	0.7–1.2	Creams, emulsions, lotions

8. Description

Carrageenan, when extracted from the appropriate seaweed source, is a yellow - brown to white colored, coarse to fine powder that is odorless and tasteless.

9. Solubility:

Lambda carrageenan is soluble in cold water as well as hot water while kappa and iota carrageenan are insoluble in cold water but their sodium salts are soluble and are soluble in hot water without sodium salts.

10. Stability and Storage Conditions

Carrageenan is a stable, though hygroscopic, polysaccharide and should be stored in a cool, dry place.

7.2. Locust Bean Gum

1. Nonproprietary Names

None adopted

2. Synonyms

Carubin, algaroba, carob bean gum, carob flour, ceratonia gum, ceratonia siliqua, ceratonia siliqua gum, cheshire gum, E410, gomme de caroube, Meyprofleur, St. John's bread.

3. Chemical Name

Carob gum

4. Empirical Formula and Molecular Weight

Ceratonia is a naturally occurring plant material that consists chiefly of a high molecular weight hydrocolloidal polysaccharide, composed of D-galactose and D-mannose units combined through glycosidic linkages, which may be described chemically as galactomannan. The molecular weight is approximately 310 000.

5. Structural Formula

Locust bean gum is a galactomannan similar to guar gum consisting of a (1-4)-linked β- D-mannopyranose backbone with branch points from their 6-positions linked to a-D-galactose (that is, 1-6-linked a-D-galactopyranose). There are about 3.5 (2.8 – 4.9) mannose residues for every galactose residue.

6. Functional Category

Controlled-release vehicle, stabilizing agent, suspending agent, tablet binder, Viscosity increasing agent.

7. Description

The highly hydrophilic LBG from the seeds of Ceratonia siliqua.

8. Typical Properties

Acidity/Alkalinity = pH = 5.3 (1% w/v aqueous solution)

Viscosity (dynamic) = 1200–2500 cP for a 1% w/v aqueous dispersion

9. Solubility

Dispersible in hot water, hydrates very slowly and incompletely in cold water & insoluble in ethanol

10. Stability and Storage Conditions

The bulk material should be stored in a well-closed container in a cool, dry place. Ceratonia loses not more than 15% of its weight on drying.

8. MATERIALS AND INSTRUMENTS

8.1. Materials used

Table.No.6 : Materials used

S. No.	Chemical and reagents	Suppliers
1	Nateglinide	Glenmark pharmaceuticals ltd.
2	K- Carrageenan	Otto kemi Pvt. ltd.
3	λ- Carrageenan	Lucid Colloids ltd.
4	Locust bean gum	Research lab – fine chem ltd.
5	Colloidal silicon dioxide	Dekkan Pharmaceuticals ltd.
6	Magnesium stearate	Loba chemie pvt. ltd.
7	Lactose monohydrate	Loba chemie pvt. ltd.
8	Polyvinyl pyrrolidone K - 30	Loba chemie pvt. ltd.

8.2 Instruments used

Table.No.7 : Instruments used

S. No.	Instrument name	SUPPLIERS/MANUFACTURERS
1	Tablet compression machine	Proton Mini Press.
2	USP Tablet Dissolution apparatus.	Lab india Analytical Instruments Pvt Ltd. Mumbai , Model-DISSO 2000.
3	UV Visible double beam spectrophotometer	LAB INDIA UV 3000+
4	Monsanto hardness tester	-
5	Roche Friability tester	-
6	Vernier Calipers	-
7	Electronic balance	Wensar PGB - 300
8	Stability Chamber	ROLEX
9	Melting point apparatus	VMP D
10	FTIR	BRUKER HTS-XT
11	Sieves	Indicot (India)
12	Tapped Density Tester	Electrolab
13	Disintegration Test Apparatus,USP	ROLEX

9. PREFORMULATION

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Preformulation studies relate to pharmaceutical and analytical investigation carried out in supporting formulation development efforts of the dosage forms.

The following preformulation studies were performed for obtained sample of drug.

9.1. ORGANOLEPTIC PROPERTIES

9.1.1. Color and nature

Transferred small quantity of the sample on a white piece of paper spreaded the powder and examined visually.

9.2. PHYSICAL CHARACTERISTICS

9.2.1. Flow properties

The flow properties of powder are critical for an efficient microsphere preparing. If the drug is identified at pre formulation stage to be "poorly flowable" the problem can be solved by selecting appropriate excipients. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Procedure

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10gm of sample powder is filled in funnel. Then funnel was open to release the powder on the paper to form a smooth conical heap, is found by measuring in a different directions. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula.

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of the repose

h = Height of the heap

r = Radius of the heap

Table.No. 8: ANGLE OF REPOSE LIMITS

ANGLE OF REPOSE	FLOWABILITY
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

9.2.2. Bulk density

Bulk density is the ratio of mass of powder to the bulk volume. Bulk density largely depends on particular shape as the particle become more spherical in shape, bulk density is increases.

Bulk density is determined by measuring the volume of a known mass of a powder sample that has been passed through a screen into a graduated cylinder.

Procedure

Bulk density of the granules was determined by pouring gently 5gms of sample through a glass funnel into a 10ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated as follows:

$$\text{Bulk Density}\left(\frac{\text{gms}}{\text{ml}}\right) = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}}$$

9.2.3. Tapped density

Tapped density is the ratio of mass of powder to the tapped volume**.**

Procedure

5 grams of granule sample was poured gently through a glass funnel into a 10ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after 50 tapping were recorded and tapped density was calculated as follows:

$$\text{Tapped Density}\left(\frac{\text{gms}}{\text{ml}}\right) = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}}$$

9.3.1. Measurement of powder compressibility

The compressibility index is measures of the propensity of a powder to be compressed. As such, they are measures relative importance of inter particulate interactions. In a free flowing powder, such interactions generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particulate interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility index calculated by the formula.

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index (I), which is determined by the following equation.

$$I\,(\%) = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped density}} \times 100$$

9.3.2. Hausner ratio

Hausner ratio is related to interparticle friction and, as such used to predict powder flow properties.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

- The compressibility index [Carr's index (%)] is an indication of changes that occur in the packing arrangement while tapping the powder and is a direct measure of the propensity of a powder to consolidate when undergoing vibration, shipping and handling. Table shows that the compressibility index was the highest for all the polymers which had poor, flow properties since higher values tend to indicate poor flowability of powders. As per Table, higher values for Hausner ratio and angle of repose indicate poor flow properties of the polymers. This data suggests the need for granulation.

Table No.9 : % Compressibility values and Hausner ratio and its significance

% Compressibility	Flow character	Hausner ratio
<10	Excellent	1.00 -1.11
11-15	Good	1.12 – 1.18
16-20	Fairly	1.19 -1.25
21-25	Passable	1.26 -1.34
26-31	Poor	1.35 – 1.45
32 -37	Very poor	1.46 -1.59
>38	Very, very poor	>1.60

9.3.3. Melting point

It is one of the parameters to judge the purity of crude drug. In case of pure chemicals, melting points are very sharp and constant**.**

Procedure

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted. The results are shown in results and discussion.

9.4. SOLUTION PROPERTIES

9.4.1. pH of the solution

Weighed and transferred accurately about 1.0 g of sample in a 200ml clean and dried beaker, dissolved in carbondioxide free water and made up the volume to 100ml with same solvent, mixed. Read the pH of freshly prepared solution by using precalibrated pH meter. The results are shown in results and discussion.

9.4.2. Solubility

A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute of vice versa. After each addition, the system is vigorously shaken and examined visually for any

undissolved solute particles. The solubility is expressed in terms of ratio of solute and solvent. The results are shown in results and discussion.

9.5. IDENTIFICATION OF DRUG AND COMPATABILITY STUDY

9.5.1. Drug –excipient compatibility studies

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

By physical observation

It was determined as per procedure given in method section the following table illustrated the result.

Table.No. 10: Physical compatibility studies

Test	Observation	Inference
Physical compatibility	No change of color	These materials are compatible for formulation

Procedure by FT-IR Studies

The IR spectrums of nateglinide with excipients were taken by preparing dispersion in dry potassium bromide under dry condition. Superimposed these spectra. The transmission minima (absorption maxima) in the spectra obtained with the sample in corresponded in position and relative size to those in the spectrum obtained with the standards.

9.6 UV SPECTROSCOPIC METHOD FOR ANALYSIS OF Nateglinide

A. UV spectroscopy: (Determination of λ max)

Nateglinide was accurately weighed and dissolved in the solvent (Phosphate buffer 6.8) to obtain solution of 100µg/ml. UV spectrum was run from 200-400nm and λ_{max} was recorded using UV spectrophotometer.

9.2.3. Preparation of calibration curve of nateglinide

Nateglinide solution of 100µg/ml was prepared in phosphate buffer pH 6.8 and UV spectrum was recorded in the wavelength range from 200-400 nm.

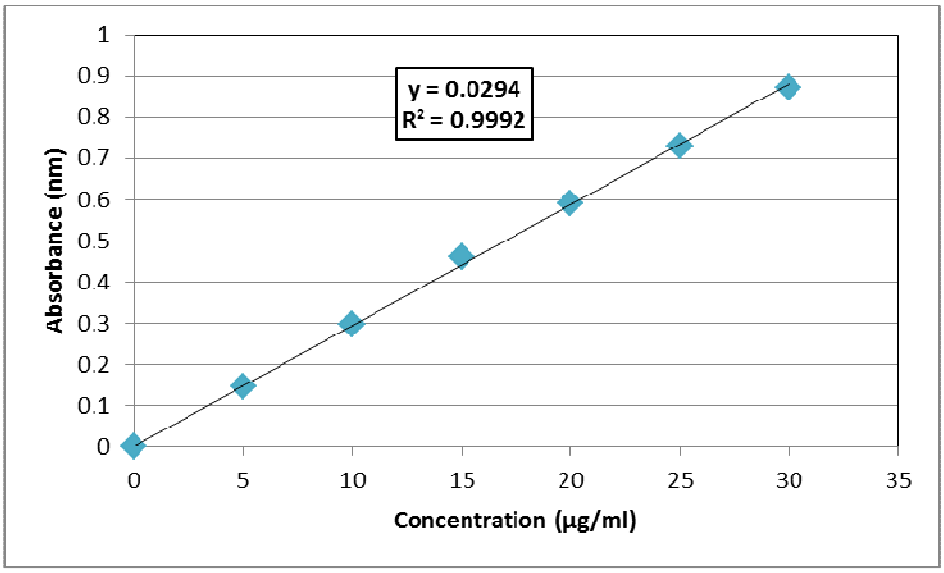
Standard stock solution: 100 mg of nateglinide was accurately weighed and transferred to 100ml volumetric flask and dissolved in phosphate buffer pH 6.8 to get solution of concentration 1000 µg/ml and this solution was further diluted suitably to get solution of concentration 50 µg/ml.

Working stock solution: A series of nateglinide solutions ranging from 5 to 30 µg/ml was prepared from standard stock solution in phosphate buffer pH 6.8. The absorbance of all solutions was measured against phosphate buffer pH 6.8 as blank at 210 nm using UV spectrophotometer. Beer's law was obeyed in the concentration range of 5-30 µg/ml. The high values of regression coefficient (0.9992) estimated the linearity of relationship between concentration and absorbance.

Table.No. 11: Calibration curve for nateglinide

S.No.	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	5	0.145
3	10	0.297
4	15	0.459
5	20	0.591
6	25	0.729
7	30	0.873
Slope	0.0294	
R^2	0.9992	

Fig.No.9: Calibration curve of nateglinide in phosphate buffer pH 6.8



10. FORMULATIONS OF SUSTAINED RELEASE MATRIX TABLETS OF NATEGLINIDE

10.1. Selection of method[116.]

A. Direct compression

The most common and simplest method available for tablet preparation is direct compression in which the drug with other excipients is mixed thoroughly with the help of various mixers followed by the compression of the resulting powder.

All the polymers selected were found to be not directly compressible, hence the wet granulation was tried.

B. Wet granulation

Wet granulation is the most famous, complex but reliable method of granulation. Most of the drugs can be granulated by this method. It includes the use of a solvent to form a wet mass of drug and excipients together followed by the drying and lubrication. In this, the drug and excipients are mixed together in a geometric progression pattern and the mixture is then wet massed with the addition of volatile solvent. This wet mass is then passed through the appropriate mesh size to obtain the granules which were dried, evaluated and finally compressed to get tablet.

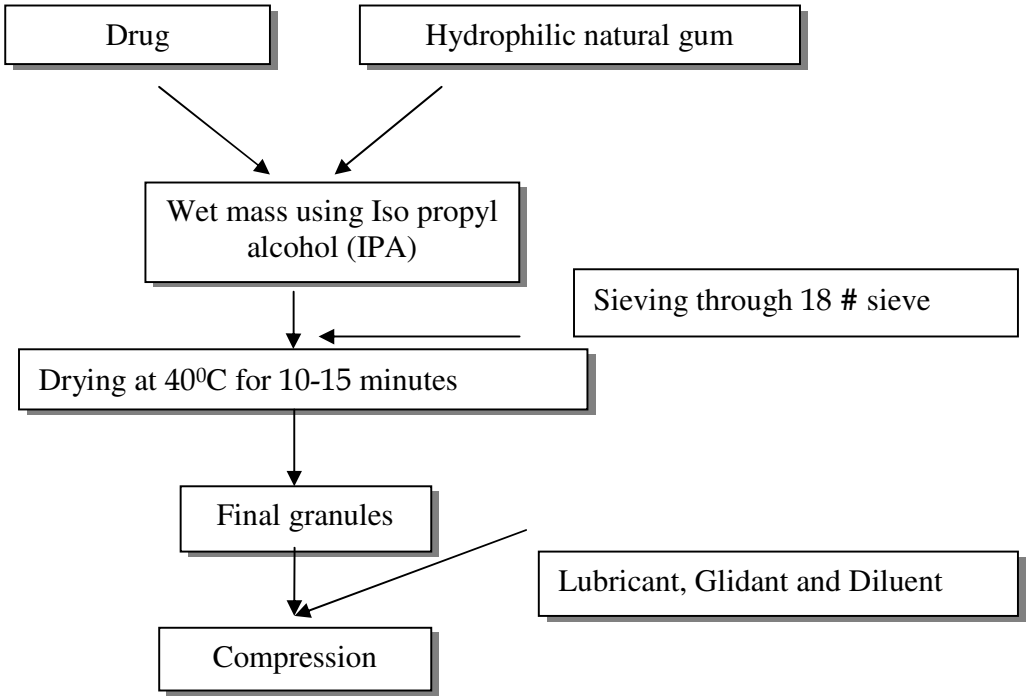


Fig..No.10: Flow diagram of wet granulation procedure

10.2. Preparation of hydrophilic matrix tablets

A. Study of various gums and its different concentration levels

The natural gums like k – carrageenan, λ - carrageenan and locust bean gum were selected for the preparation of tablets and their concentrations in the formulations ranging from different ratios were used.

B. Procedure for preparation of matrix tablet[117]:

- Accurately weighed quantity of drug (nateglinide) and polymer were passed through 40# sieve.
- The polymer and the drug were then mixed in a mortar by geometric progression for a period of 10-15 minutes.
- This mixture was then granulated with isopropyl alcohol, and sieved using 18# sieve. Obtained granules were then dried in hot air oven at 40^0C for 10-15 minutes.
- The dried granules were mixed with magnesium stearate and colloidal silicon dioxide and lactose monohydrate for further 2 minutes and compressed under 10mm std. concave punch.

10.2. 1. K – carrageenan

Table No.12: Composition of k - carrageenan based matrix tablets of nateglinide

Ingredients	**F_1**	**F_2**	**F_3**
Nateglinide	120	120	120
K - carrageenan	90	105	120
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	78	63	48
PVP K – 30	6	6	6

*All the quantities are in mg

10.2. 2. λ- carrageenan

Table No.13: Composition of λ- carrageenan based matrix tablets of nateglinide

Ingredients	**F_4**	**F_5**	**F_6**
Nateglinide	120	120	120
λ- carrageenan	90	105	120
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	78	63	48
PVP K – 30	6	6	6

*All the quantities are in mg

10.2. 3. Locust bean gum

Table No.14: Composition of locust bean gum based matrix tablets of nateglinide

Ingredients	**F_7**	**F_8**	**F_9**
Nateglinide	120	120	120
Locust bean gum	90	105	120
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	78	63	48
PVP K – 30	6	6	6

*All the quantities are in mg

10.2.4. K – carrageenan + Locust bean gum

A. K – carrageenan + Locust bean gum combinations

From the results obtained by previous studies carried out using individual k – carrageenan

(F_1 – F_3) and locust bean gum as hydrophilic matrix (F_7 – F_9), the percentage in which the k - carrageenan and locust bean gum combination could be used to formulate once a

day formulation of nateglinide was selected. The proportions of gum selected were 20:80, 40:60, 50:50, 60:40, 80:20 as mentioned in the table no. 11. These ratios are in percentages of dry polymer weight i.e. 20% of k – carrageenan and 80% of locust bean gum in F_{10} and likewise for other ratios.

Table No.15: Composition of k - carrageenan + locust bean gum combinations based matrix tablet of nateglinide

Ingredients	F_{10} (20:80)	F_{11} (40:60)	F_{12} (50:50)	F_{13} (60:40)	F_{14} (80:20)
Nateglinide	120	120	120	120	120
K – carrageenan	24	48	60	72	96
Locust bean gum	96	72	60	48	24
Colloidal silicon dioxide	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose monohydrate	48	48	48	48	48
PVP K - 30	6	6	6	6	6

*All the quantities are in mg

B. K - carrageenan + Locust bean gum 40:60 combinations

From the results obtained in above study, 40:60 ratio of k – carrageenan: locust bean gum in F_{41} was chosen to reduce the total polymer concentration from the tablet. Now, formulations were formulated such that each formulation contains 12mg less polymer content than previous formulation. It means from F_{45} to F_{49}**,** there is 10% less polymer concentration in each formulation i.e. F_{46} contains 12mg less polymer content than F_{45} and so on, to obtain the formulation giving once a day formulation of nateglinide containing least amount of polymer.

Table No.16: Composition of k – carrageenan + locust bean gum 40:60 combinations based matrix tablets of nateglinide

Ingredients	F_{15}	F_{16}	F_{17}	F_{18}	F19
Nateglinide	120	120	120	120	120
K - carrageenan	21.6	19.2	16.8	14.4	12
Locust bean gum	86.4	76.8	67.2	57.6	48
Colloidal silicon dioxide	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose monohydrate	60	72	84	96	108
PVP K - 30	6	6	6	6	6

*All the quantities are in mg

λ – carrageenan + Locust bean gum

A. λ – carrageenan + Locust bean gum combinations

From the results obtained by previous studies carried out using individual λ - carrageenan ($F_4 – F_6$) and locust bean gum as hydrophilic matrix ($F_7 – F_9$), the percentage in which the λ – carrageenan and locust bean gum combination could be used to formulate once a day formulation of nateglinide was selected. The proportions of gums selected were 20:80, 40:60, 50:50, 60:40, 80:20 as mentioned in the table no. 13. These ratios are in percentages of dry polymer weight i.e. 20% of λ – carrageenan and 80% of locust bean gum in F_{20} and likewise for other ratios.

Table No.17: Composition of λ - carrageenan + locust bean gum combinations based matrix tablets of nateglinide

Ingredients	F_{20} (20:80)	F_{21} (40:60)	F_{22} (50:50)	F_{23} (60:40)	F_{24} (80:20)
Nateglinide	120	120	120	120	120
λ – carrageenan	24	48	60	72	96
Locust bean gum	96	72	60	48	24
Colloidal silicon dioxide	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose monohydrate	48	48	48	48	48
PVP K – 30	6	6	6	6	6

*All the quantities are in mg

B. λ - carrageenan + Locust bean gum 20:80 combinations

From the results obtained in above study, 20:80 ratio of λ – carrageenan: locust bean gum in F_{20} was chosen to reduce the total polymer concentration from the tablet. Now, formulations were formulated such that each formulation contains 12mg less polymer content than previous formulation. It means from F_{25} to F_{27}**,** there is 10% less polymer concentration in each formulation i.e. F_{26} contains 12mg less polymer content than F_{25} and so on, to obtain the formulation giving once a day formulation of nateglinide containing least amount of polymer.

Table No.18: Composition of λ – carrageenan + locust bean gum 20:80 combinations based matrix tablets of nateglinide

Ingredients	F_{25}	F_{26}	F_{27}
Nateglinide	120	120	120
λ – carrageenan	21.6	19.2	16.8
Locust bean gum	86.4	76.8	67.2
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	60	72	84
PVP K – 30	6	6	6

*All the quantities are in mg

11. EVALUATION OF MATRIX TABLETS OF NATEGLINIDE

a) Pre-compression Studies: Micromeritic properties

i) Angle of repose

5 gms of the sample was taken in a funnel fixed in a holder (6 cm) above the surface at an appropriate height and graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and angle of repose was determined using the above formula. This was repeated five times for a sample.

$$\theta = \tan^{-1}(h/r)$$

Where,

h = height

r = radius

θ= angle of repose

The results are given in results and discussion.

ii) Determination of bulk density and tapped density

A quantity 5gm of the powder (W) from each formula was introduced in to a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density and tapped density were calculated using the following the formula

$$\text{Bulk density } (\rho_b) = m/V_b$$

$$\text{Tapped density}(\rho_t) =) = m/V_t$$

Where,

m = mass of the powder

V_b = initial or bulk volume

V_t = final or tapped volume

The results are given in results and discussion.

iii) Measurement of compressibility index and Hausner ratio

Compressibility index and Hausner ratio are measured by using the following formula

$$\%\ \text{compressibility (carr's index)} = \frac{\text{Tapped density - Intial bulk density}}{\text{Tapped density}} \times 100$$

The result is given in in results and discussion.

$$\text{Hausner ratio} = V_b / V_t$$

Where,

V_b = initial or bulk volume

V_t = final or tapped volume

The results are given in results and discussion.

11. Evaluation of matrix tablet

11.1. Physical characterization of tablet

A. Hardness[114]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

B. Thickness [114]

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier Calipers .

C. Friability [114]

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss } = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}}$$

D. Uniformity of Weight[118]

Weigh 10 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in Table No. 15 and none deviates by more than twice that percentage.

Table No.19. IP Standards of Uniformity of weight

Sr. No.	Avg. wt. of tablet	% of deviation
1	80 mg or < 80	10
2	> 80 to < 250 mg	7.5
3	> 250 or more	5

E. Determination of drug content [119]

- Five tablets were weighed individually, then placed in a mortar and powdered with a pestle.
- An amount equivalent to 50 mg drug (750 mg) was extracted in phosphate buffer pH 6.8 and shaken for 15 minutes.
- The 2ml of this solution was again diluted to 10ml with phosphate buffer pH 6.8. This solution was then analyzed spectrophotometrically at 210nm.

11.2. *Invitro* studies

- The USP type II dissolution apparatus was used to for vitro drug release study utilizing Dissolution System Lab india Analytical Instruments Pvt Ltd. Mumbai with a constant temperature water bath at $37^0C \pm 1^0C$.
- The dissolution medium used was 0.2M phosphate buffer pH 6.8 (900ml) and the speed of rotation was kept 50 rpm.
- 6 ml of samples were collected after 1 hr. time interval and analyzed using UV spectrophotometer at 210 nm.

- Studies were performed in duplicate and the mean cumulative percentage of drug calculated (SD) and plotted against time.

11.3. Determination of drug release kinetics

To describe the kinetics of the drug release from the sustained release matrix tablets, mathematical models such as Zero-order, First-order, Higuchi & Korsmeyer-peppas models the release data were evaluated by model-dependent (curve fitting) method. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

Zero-order kinetic model –Cumulative % drug released vs. time

First order kinetic model -log cumulative % drug remaining vs. time

Higuchi model -Cumulative % drug released vs. square root of time

Korsemeyer-peppas model -log cumulative % drug released vs. log time

Zero order- kinetic model

Zero order release would be predicted by the following equation.

$$A_t = A_o - K_o t$$

Where,

A_t - Drug release at time‘t’

A_o- Initial drug concentration

K_o - Zero order rate constant (hr^{-1})

When the data plotted as cumulative % drug release Vstime and the plot is linear , then the data obeys Zero-order equal to K_o.

First order kinetics

First order release would be predicted by the following equation

$$LogC = logC_o - K_t/2.303$$

Where,

Log C - Amount of drug remained at time ‘t’

$logC_o$ - initial drug concentration

K - first order rate constant (hr^{-1})

When the data plotted as log cumulative % remaining Vs time yields a straight line, then the release obeys first order kinetics. The constant 'K' obtained by multiplying 2.303 with the slope values.

Korsemeyer-peppas model.

To study the mechanism of drug release from microspheres, the *invitro* data were fitted to the well known exponential equation (korsemeyerpeppasmodel) which is often used to describe the drug release behavior from polymeric systems.

$$Mt/M\alpha = Kt^n$$

Where,

Mt/Mα - The fraction of drug released at 't'

K - Constant incorporating structural and geometrical characteristics of the drug / polymer system

n - Diffusion exponent related to mechanism the drug release

When the data plotted as log % drug released Vs log time yields a straight line with a slope equal to 'n' and the K can be obtained by y- intercept.

Mechanism of drug release as per korsemeyer-peppas equation / peppas model

Table 20.Mechanism of drug release

S . No	n values	Drug release
1	0-0.5	Fickian release
2	0.5-1.0	Non-Fickian release
3	>1.0	Class II transport

12. RESULTS AND DISCUSSIONS

PRE FORMULATION STUDIES

Organoleptic properties

These tests were performed as procedure given, Preformulation part. The results are illustrated in following table.

Table 21. Organoleptic properties

Test	Specifications/limits	Observations
Color	White, Crystalline powder	White, Crystalline powder
Odour	Odorless, Bitter taste	Odorless, Bitter taste

The results complies as per specifications

Angle of repose

It was determined as per procedure preformulation in material and method part. The results are illustrated in following table**.**

Table 22. Flow properties

Material	Angle of repose
Nateglinide	27°.14”

The result shows that drug having poor flow

Bulk density and tapped density.

It was determined as per procedure given preformulation in material and method part. The results are illustrated in table**.**

Table 23. Density

Materials	Bulk Density(gm/ml)	Tapped density(gm/ml)
Nateglinide	0.19	0.26

Powder compressibility

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in table**.**

Table 24. Powder compressibility

Material	Compressibility index	Hausner ratio
Nateglinide	31.42%	1.18

The results shows that drug having poor flow property

Melting point

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in following table**.**

Table 25. Melting point

Material	Material point range	result
Nateglinide	137 ℃	Complies

The result complies as per specification.

SOLUTION PROPERTIES

pH of the solution

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in following table**.**

Table 26. pH

Material	Test	Specification	Observation
Nateglinide	pH	6.5	6.5

The result complies as per specification

Solubility

It was determined as per procedure given in preformulation in material and method part. The results are illustrated in following table.

Table 27. Solubility

Test	Specification	Result
solubility	soluble in methanol, ethanol, chloroform, dissolved in acetone, ethyl ether, almost insoluble in water.	Complies

The result complies as per specification.

DRUG-EXCIPIENT COMPATABILITY STUDIES

Discussion:

Drug excipient interactions play a vital role with respect to release of drug from formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipient used.

Table 28. Drug – Excipients Compatibility Study Results

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + K- Carrageenan	White powder	No change	No change	Yes
Drug + λ- Carrageenan	White powder	No change	No change	Yes
Drug + Locust bean gum	White powder	No change	No change	Yes
Drug + Excipients	White powder	No change	No change	Yes

IR GRAPHS

Fig. 11(a) FT-IR of Nateglinide

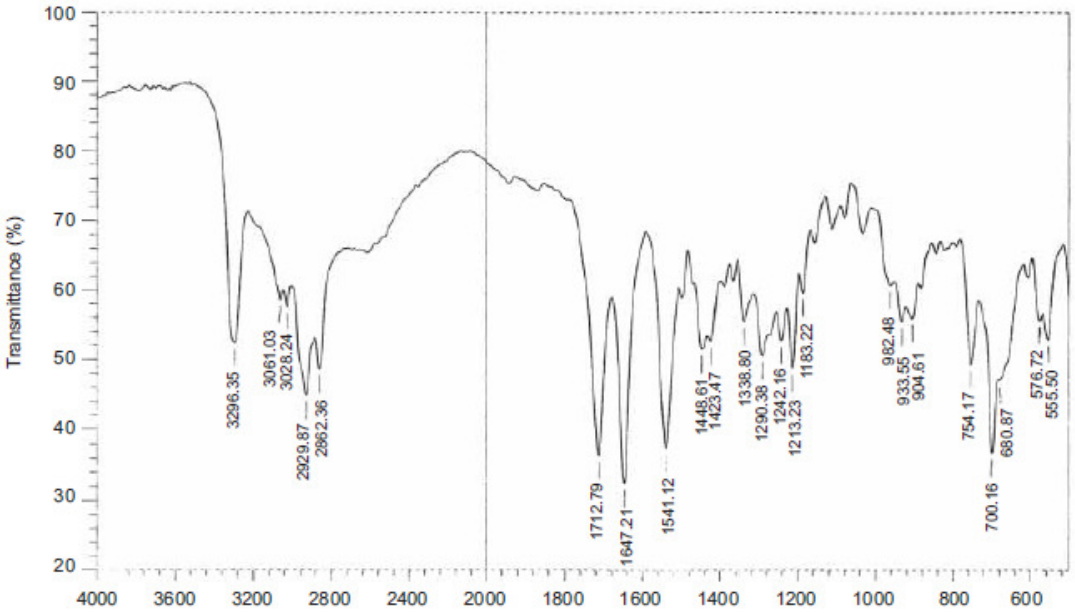


Fig. 11(b) FT-IR Graph of Formulation

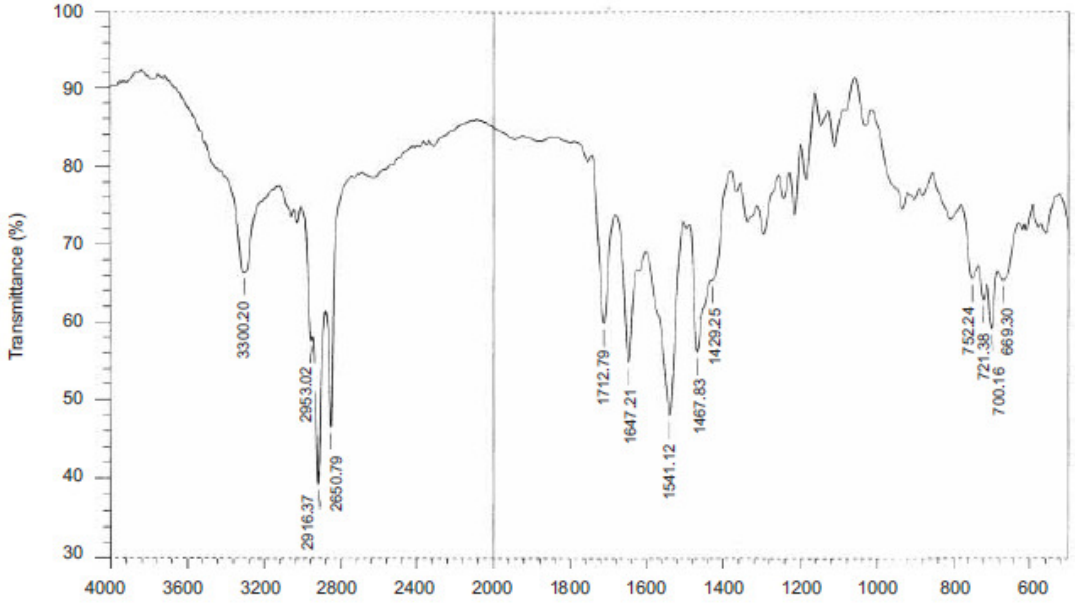


Table.No.29: Band Assignments for the Infrared Absorption Spectrum of Nateglinide

Band Energy (cm-1)	Assignment
1280 - 1431	carboxyl, carboxylate
1651	carbonyl
2866 - 3047	C-H stretching
1714	C=O
3298	N-H stretching
1296	C-O stretching
1446	C-O-H stretching
3296 - 3311	N-H stretching

In the present study, it has been observed that there is no chemical interaction between nateglinide and the polymers used. From the figures 11(a) and 11(b) it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymer.

PRECOMPRESSION STUDIES:

EVALUATION OF TABLETS:

Table No 30: EVALUATION OF GRANULES:

Batch NO.	Angle of Repose(°)	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (%)	Huasner Ratio
F1	21°32′	0.2574	0.3201	10.17	1.09
F2	22°54′	0.2641	0.3279	10.31	1.07
F3	21°52′	0.2678	0.3245	9.96	1.08
F4	28°37′	0.2745	0.3360	10.12	1.07
F5	27°31′	0.2792	0.3374	14.78	1.12
F6	26°87′	0.2748	0.3350	13.89	1.16
F7	24°63′	0.2749	0.3369	13.97	1.14
F8	24°67′	0.2801	0.3374	13.45	1.13
F9	23°14′	0.2841	0.3403	13.78	1.11
F10	25°47′	0.2814	0.3407	14.07	1.09
F11	26°92′	0.2874	0.3464	14.74	1.09
F12	24°85′	0.2799	0.3542	14.07	1.16
F13	25°03′	0.2745	0.3571	14.95	1.11
F14	24°31′	0.2868	0.3498	14.64	1.12

Table No 31: EVALUATION OF GRANULES:

Batch NO.	Angle of Repose(°)	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (%)	Huasner Ratio
F15	26°03′	0.2823	0.3123	09.32	1.12
F16	26°47′	0.2831	0.3214	10.95	1.13
F17	27°09′	0.2932	0.3675	10.47	1.14
F18	26°91′	0.2945	0.3374	11.31	1.12
F19	27°33′	0.2846	0.3235	12.29	1.09
F20	27°93′	0.2753	0.3492	12.45	1.17
F21	28°17′	0.2785	0.3345	12.78	1.16
F22	28°54′	0.2714	0.3975	12.64	1.18
F23	29°08′	0.2681	0.3374	13.74	1.11
F24	28°02′	0.2574	0.3312	13.17	1.13
F25	26°51′	0.2968	0.3607	14.71	1.12
F26	26°75′	0.2734	0.3471	14.46	1.16
F27	27°92′	0.2789	0.3682	14.09	1.17

Discussion

The angle of repose for the formulations F1-F27 was found to be in the range 21°32′ to 29°08′ shows good flow property

Compressibility index for the formulations F1-F10 found between 09.32% to 14.95% indicating the good flow property.

Huasner Ratio for the formulations F1-F10 found between 1.07 to 1.18 indicating the good flow property.

EVALUATION OF NATEGLINIDE TABLETS:

Table. No: 32.WEIGHT VARIATION AND FRIABILITY:

Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)
F1	301±1.52	0.21	4.12±0.2	8.07
F2	304±2.37	0.23	4.03±0.2	7.92
F3	298±1.44	0.33	4.22±0.1	8.14
F4	320±1.86	0.42	4.31±0.1	7.54
F5	312±2.56	0.41	4.07±0.1	7.92
F6	303±2.13	0.23	4.12±0.1	7.61
F7	304±1.52	0.24	4.06±0.2	7.47
F8	318±1.49	0.20	4.19±0.3	7.42
F9	290±2.37	0.18	4.38±0.2	8.10
F10	312±1.91	0.25	4.12±0.1	8.32
F11	309±1.34	0.24	4.16±0.2	8.23
F12	317±2.03	0.35	4.14±0.2	8.14
F13	309±1.92	0.27	4.23±0.2	7.76
F14	303±1.66	0.52	4.08±0.1	7.91

Table. No: 33.WEIGHT VARIATION, FRIABILITY THICKNESS & HARDNESS

Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)
F15	320±2.12	0.16	4.01±0.1	8.09
F16	309±1.03	0.34	4.03±0.1	8.32
F17	314±1.47	0.31	4.12±0.2	8.14
F18	306±1.42	0.24	4.62±0.3	8.45
F19	313±2.03	0.23	4.03±0.1	8.15
F20	312±1.74	0.29	4.08±0.2	7.92
F21	303±1.92	0.41	4.31±0.2	7.65
F22	291±2.04	0.36	4.26±0.1	8.19
F23	289±1.92	0.24	4.12±0.3	8.74
F24	301±1.25	0.31	4.14±0.2	8.31
F25	316±1.36	0.17	4.19±0.2	8.47
F26	303±1.23	0.24	4.27±0.1	8.23
F27	301±1.82	0.29	4.21±0.1	8.35

Discussion:

The weight variation of the tablet in the range of ± 1.03 % to ± 2.37 % (below 5%) complying with pharmacopoeial specification.

The friability of the tablet in the range of 0.16 % to 0.52% (below 1%) complying with pharmacopoeial specifications.

The thickness of the formulations from F1- F12 was found to be in the range of 4.01±0.1 to 4.31±0.2 and hardness of the formulated tablets was found to 7.42 to 8.74 indicating a satisfactory mechanical strength for the sustained release.

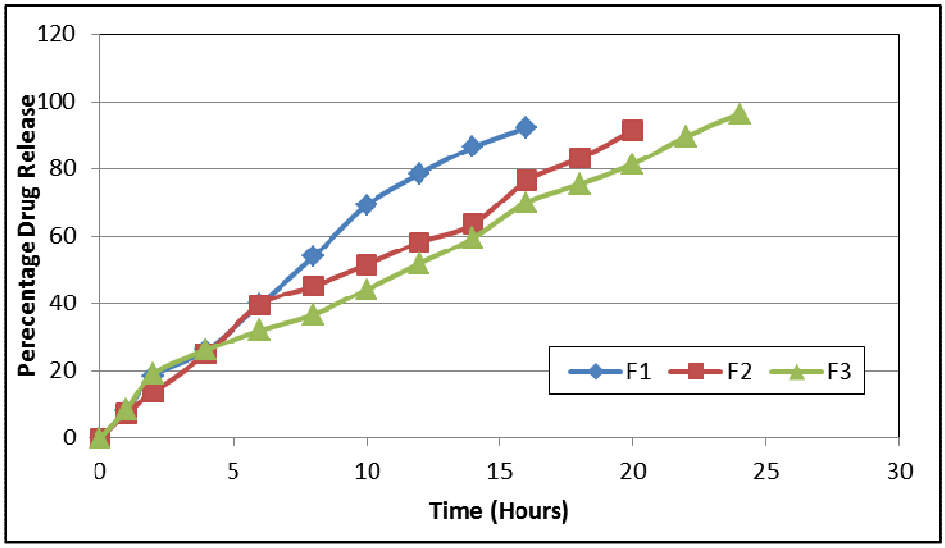
12.1.2. K – Carrageenan

The drug release from the k – carrageenan matrices is dependent upon the extent of swelling and the formation of gel layer on the matrices. As the concentration of k – carrageenan increases in matrix from F_1 – F_3, the extent of swelling and the thickness and viscosity of the gel layer increases. The inverse relationship between drug release and swelling was observed. Initially drug release from k – carrageenan matrices was slow due to rapid hydration and swelling of the matrices. F_3 shows the once a day release from the matrix tablet while, F_1 & F_2 showed the premature drug release. It was found that as the amount of gum in the matrix increased, there was a greater degree of gum hydration with simultaneous swelling. This would result in lengthening of the drug diffusion pathway and drug release rate would go on decreasing. This is due to the fact that the erosion rate from F_2 & F_3 matrices was very fast as compared to F_3 as it contains lower concentration of polymer.

Table.No. 34. In vitro drug release profile of F_1 – F_3

Time (hours)	BATCH NO.		
	F1	F2	F3
1	8.20	7.48	8.53
2	18.39	13.52	19.03
4	26.08	25.11	26.15
6	39.72	39.58	31.96
8	53.79	45.09	36.61
10	69.13	51.44	44.13
12	78.51	58.19	51.83
14	86.40	63.52	59.44
16	92.16	76.43	69.97
18		83.10	75.44
20		91.30	81.39
22			89.55
24			96.21

Fig 12. In vitro drug release profile of $F_1 – F_3$



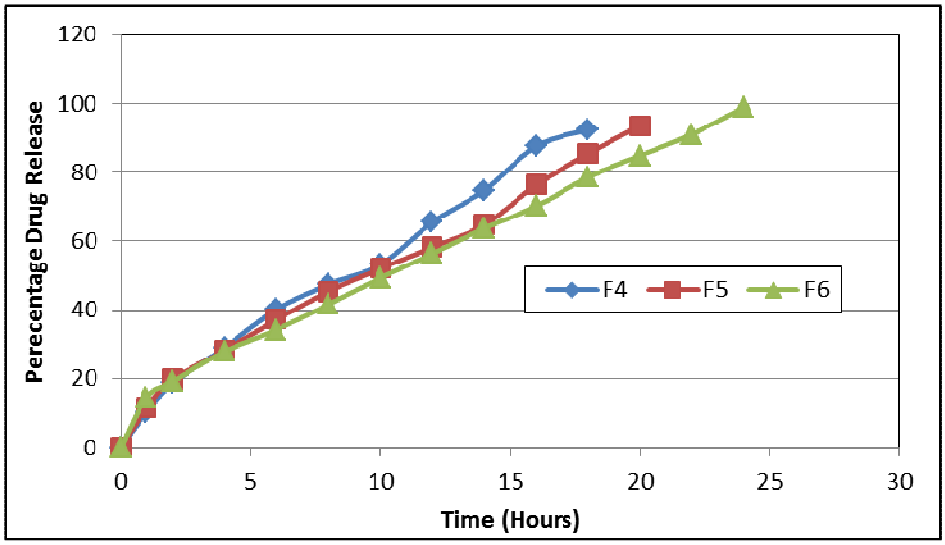
12.1.3 λ – Carrageenan

The drug release from the λ - carrageenan matrices is dependent upon the extent of swelling of the matrices. As the concentration of λ – carrageenan increases in matrices from $F_4 – F_6$, swelling increases and drug release rate decreases from the matrices i.e. there was an inverse relationship between drug release and swelling. Initially drug release from λ – carrageenan matrices was slow due to rapid hydration and swelling of the matrices. F_6 showed the once a day release and F_4 and F_5 showed the premature drug release. The λ – carrageenan matrices do not shows the gelation capacity hence the drug release from these matrices does not depends upon the gel layer formation but on extent of swelling. Matrix erodibility is related to polymer solubility, also seems to be a useful property for obtaining linear drug release profiles. In fact, matrix erosion limits the increase in the diffusional pathway and avoids the decrease of release rate with time. It is also conceivable that the higher the percentage of λ- carrageenan in the formulation, the stronger the effect of its dissolution behaviour on the attrition rate of the matrix.

Table.No. 35. In vitro drug release profile of $F_4 – F_6$

Time (hours)	BATCH NO.		
	F4	F5	F6
1	10.32	11.59	14.53
2	18.69	19.77	19.22
4	29.03	28.13	27.90
6	40.12	37.12	34.22
8	47.39	45.33	41.56
10	53.12	51.97	49.29
12	65.44	58.20	56.33
14	74.70	64.66	63.70
16	87.53	76.23	70.08
18	92.39	85.40	78.54
20		93.56	84.89
22			91.05
24			98.89

Fig 13. In vitro drug release profile of F4-F6



12.2. Locust bean gum [LBG]

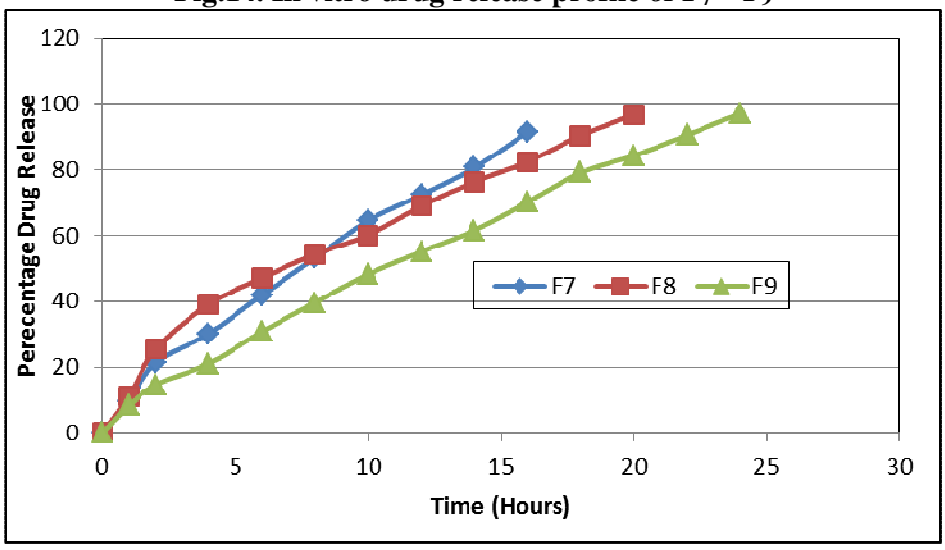
The drug release from the LBG matrices is dependent upon the gel layer thickness and viscosity of the gel layer. Being hydrophilic in nature, LBG, after hydration and swelling, goes into solution or erodes. Thus, the overall dimensions of the matrices are

affected by the rate of swelling and that of dissolution/erosion. As the concentration of the LBG increases in the matrix from F_7 – F_9, the diameter of the tablet was found to increase progressively and a distinct gel-sol boundary develops and the rate of erosion decreases due to formation of viscous and thick gel layer. Hence, retardation of drug release increases from the matrices F_7 – F_9. In the case of LBG matrices, a rate of erosion of the hydrated layer was significant as compared to other galactomannans (guar gum), thus requiring 40% polymer concentration to retard the drug release for 24hrs.

Table.No. 36. In vitro drug release profile of F_7 – F_9

Time (hours)	BATCH NO.		
	F7	F8	F9
1	09.68	11.27	08.32
2	21.33	25.41	14.71
4	30.21	39.17	21.07
6	41.96	47.14	30.82
8	53.22	54.41	39.71
10	64.56	60.19	48.27
12	72.39	69.02	55.14
14	80.66	76.41	61.63
16	91.53	82.50	70.24
18		90.47	79.14
20		96.74	84.33
22			90.56
24			97.19

Fig.14. In vitro drug release profile of F_7 – F_9



12.2.1K – carrageenan + Locust bean gum

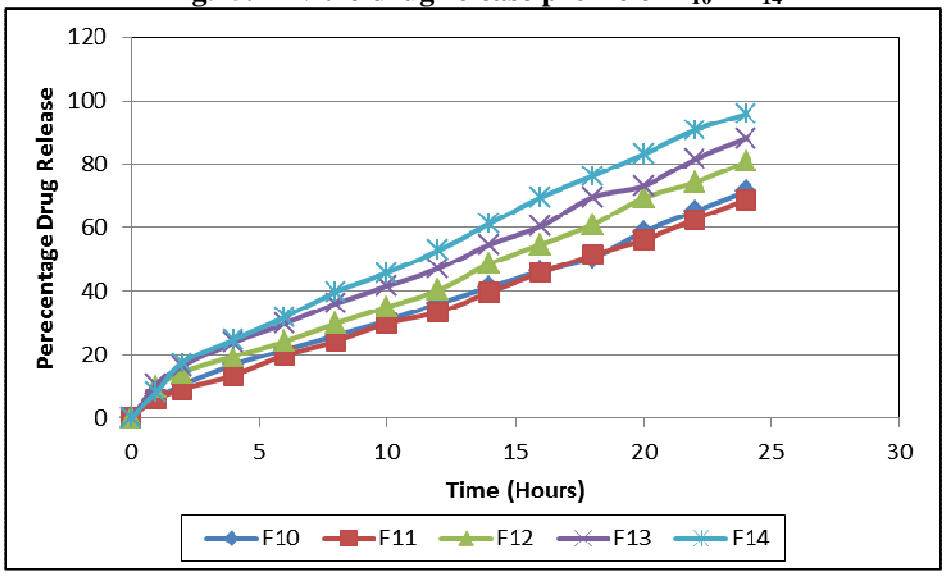
A. K – carrageenan + Locust bean gum combinations

K – carrageenan and locust bean gum are swellable gel forming polymers. On contact with aqueous medium k – carrageenan and locust bean gum matrix gradually begins to hydrate from the periphery towards the centre, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium. The hydrated gel layer thickness determines the diffusional path length of the drug. The in vitro drug release profiles of nateglinide from matrices containing k – carrageenan and locust bean gum in different gum proportions (F_{10} – F_{14}) were shown in fig.. From the fig., it is clear that, the drug release was more retarded in k – carrageenan and locust bean gum combination matrices than individual k – carrageenan (F_1 – F_3)and locust bean gum matrices (F_7 – F_9). K – carrageenan swells fast initially and forms gel quickly and locust bean gum swells slowly and steadily. From the fig., it can be seen that, the maximum retardation of drug has been observed in F_{10} which contains the 40:60 ratio of k – carrageenan: locust bean gum. This might be due to the synergistic interaction between these two gums to produce a strong and elastic gel around the core of the matrices retarding the drug release from the matrices. As we go on increasing or decreasing the concentration of k – carrageenan or locust bean gum, the retardation efficiency of drug release from the matrices was found to go on decreasing. This might be due to the fact that the synergistic interaction between two gums goes on decreasing as we increased either of gum concentration in formulation. As the locust bean gum concentration decreases in F_{10} from F_{11} there is increase in drug release from 68.88% (F_{11}) to 71.45% (F_{10}) at t_{24}h. It was found that there was not much increase in drug release in F_{10}. This might be due to the fact that there was not much decrease in synergistic interaction, ultimately not reducing the thickness and viscosity of the gel layer to a much extent. When the k – carrageenan concentration was increased from F_{11} to F_{14}, it was observed that the drug release from the matrix was increased from 68.88% (F_{11}) to 80.75% (F_{12}), 88.15 (F_{13}), and 95.87% (F_{14}) at t_{24}h. This increased drug release from F_{11} to F_{14} might be due the fact that k – carrageenan and might be due to the formation of less strong and elastic gel.

Table.No. 37. In vitro drug release profile of F_{10} – F_{14}

Time (hours)	BATCH NO.				
	F10	F11	F12	F13	F14
1	6.24	05.93	09.62	10.47	8.21
2	10.41	09.14	14.27	16.21	17.43
4	16.70	13.42	19.43	23.83	24.71
6	21.51	19.74	24.17	29.72	31.84
8	26.07	24.34	29.82	36.14	39.81
10	30.74	29.91	35.07	41.57	45.77
12	36.14	33.40	40.33	47.13	52.86
14	41.29	39.72	48.64	54.71	61.28
16	46.30	45.81	54.73	60.43	69.56
18	50.47	51.34	60.81	69.57	76.25
20	58.67	56.17	69.40	73.14	83.17
22	65.12	62.55	74.21	81.57	90.74
24	71.45	68.88	80.75	88.15	95.87

Fig.15. In vitro drug release profile of F_{10} – F_{14}



B. K - carrageenan + Locust bean gum 40:60 combinations

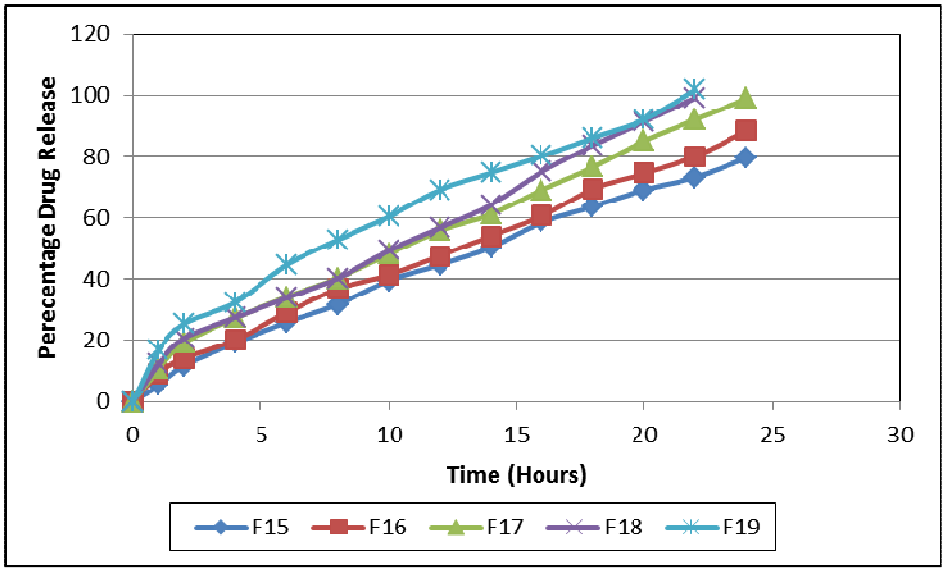
It is clear that the drug release from the k – carrageenan and locust bean gum combination matrices depends upon the formation of gelatinous swollen mass and its thickness which determines the diffusional path length of the drug to diffuse out from the

matrix into dissolution medium. The in vitro drug release profiles of nateglinide from k – carrageenan and locust bean gum combination matrices (F_{15} – F_{19}) are shown in fig. From the fig, it can be clearly seen that, as the concentration of total dry polymer decreases in the formulation, the drug release from the matrix goes on increasing. This suggests that there is inverse relationship between drug release and polymer concentration. As the polymer concentration decreases in the matrix, the formation of swollen gelatinous mass and thickness of that formed swollen mass decreases. This might be the reason for the increased drug release from the matrix. The drug release from the formulations F_{15} – F_{17} is 79.51% (F_{15}), 88.44% (F_{16}) and 98.90% (F_{17}) at t_{24}h and 99.21% (F_{18}) at t_{22}h and 101.83% (F_{19}) at t_{20}h. As the formulation F_{17} showed the drug release upto t_{24}h i.e. it formed the once a day sustained release formulation of nateglinide. This means that the 30% (36mg) of polymer concentration of was reduced from the formulation.

Table.No. 38. In vitro drug release profile of F_{15} – F_{19}

Time (hours)	BATCH NO.				
	F15	**F16**	**F17**	**F18**	**F19**
1	05.31	09.17	10.71	12.42	16.88
2	11.78	14.24	19.22	20.71	25.40
4	19.26	20.14	27.34	27.48	32.46
6	25.87	29.14	34.19	33.85	44.58
8	31.74	36.72	40.28	40.24	52.86
10	39.45	41.34	48.17	49.33	60.44
12	44.67	47.60	55.83	56.81	69.14
14	50.41	54.12	61.24	64.27	74.65
16	58.62	60.71	69.17	75.08	80.19
18	63.77	69.48	76.57	83.72	86.17
20	69.12	74.52	85.14	91.47	92.12
22	73.20	80.12	92.12	99.21	101.83
24	79.51	88.44	98.90		

Fig.16. In vitro drug release profile of F_{15} – F_{19}



12.2.2 λ – carrageenan + Locust bean gum

A. λ – carrageenan + Locust bean gum combinations

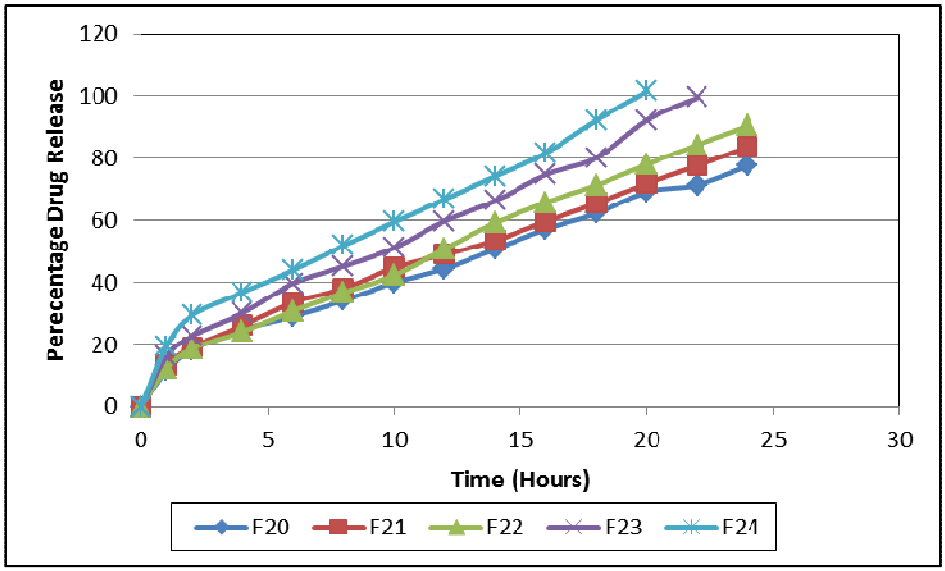
Carrageenans are a group of sulphated polymers consisting of galactose residues. The degree of sulphate esterification especially affects the gelation properties of the polymer. In particular, λ - carrageenan has a higher degree of esterification, does not show gelation capability but it hydrates and swells to a good extent. Locust bean gum is swellable gel forming polymer. Hence, by combining these two polymers they formed swellable gelatinous layer. The hydrated gel layer thickness determines the diffusional path length of the drug and ultimately the drug release. The in vitro drug release profiles of nateglinide from tablets containing λ – carrageenan and locust bean gum in different gum proportions (F_{20} – F_{24}) are shown in fig.17. From the fig.17, it is clear that, the drug release was more retarded in λ – carrageenan and locust bean gum combination matrices (F_{20} – F_{24}) than individual λ – carrageenan (F_4 – F_6) and locust bean gum matrices (F_7 – F_9). As mentioned above λ- carrageenan hydrates and swells fast but it do not forms the gel. Hence, the drug release initially controlled due to the swelling of λ- carrageenan and then the formation of swellable gelatinous layer by locust bean gum. From the fig.17, it can be seen that, the maximum retardation of drug has been observed in F_{20} which contains the 20:80 ratio of λ – carrageenan: locust bean gum. This might be due to the

synergistic interaction between these two gums to produce a strong and elastic gel around the core of the matrices retarding the drug release from the matrices. From the in vitro release profile of $F_{20} – F_{24}$ it can be seen that, as we increased the concentration of the λ – carrageenan from formulation ($F_{20} – F_{24}$), the drug release from the matrices increased. When the λ – carrageenan concentration was increased from F_{20} to F_{24}, it has been observed that the drug release from the matrix was increased from 77.68% (F_{20}) to 83.65% (F_{21}), 90.40% (F_{22}) at t_{24}h and 99.6% (F_{23}) at t_{23}h and 101.63% (F_{24}) at t_{20}h. As the λ – carrageenan does not form gel but swells hence; erosion is predominant with it as compared to the swellable gel forming polymers such as locust bean gum. Also, as the λ – carrageenan concentration increases in the formulation, locust bean gum concentration decreases, the thickness and the viscosity of the gel layer around the tablet decreases. This might be the contributing factor for the increased drug release from $F_{20}– F_{24}$.

Table.No. 39. In vitro drug release profile of $F_{20} – F_{24}$

Time (hours)	BATCH NO.				
	F20	**F21**	**F22**	**F23**	**F24**
1	11.78	13.37	12.44	16.41	19.74
2	18.35	19.12	18.75	22.77	29.45
4	24.89	26.22	24.22	30.22	36.88
6	29.08	33.64	30.95	39.72	43.95
8	34.24	38.09	36.74	45.21	51.93
10	39.96	44.78	42.33	51.17	59.48
12	44.47	49.08	50.87	59.84	66.85
14	50.78	53.57	59.24	66.30	74.24
16	57.20	59.74	65.85	74.81	81.75
18	62.28	65.51	71.39	80.17	92.24
20	69.14	71.92	78.09	92.28	101.63
22	71.45	77.69	84.33	99.61	
24	77.68	83.65	90.40		

Fig.17. In vitro drug release profile of F_{20} – F_{24}



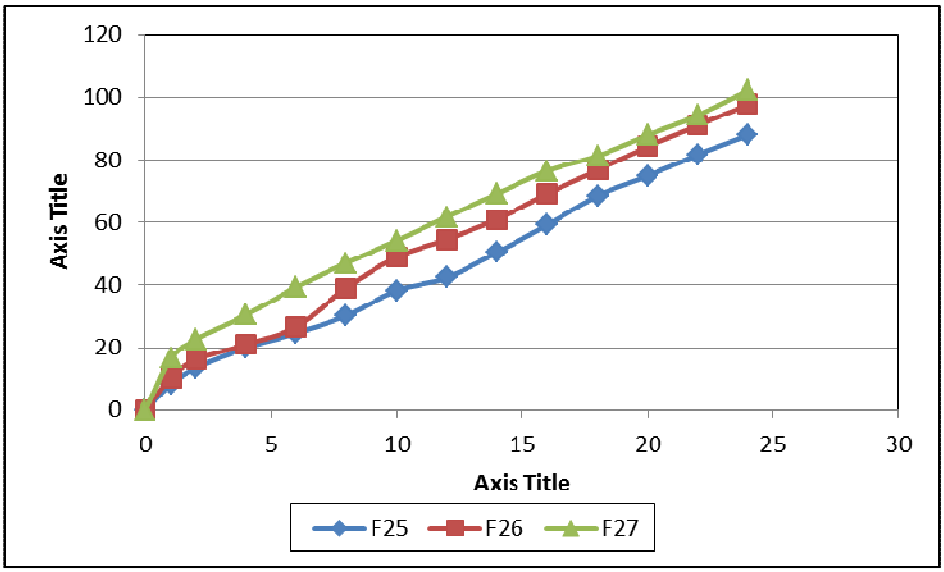
B. λ - carrageenan + Locust bean gum 20:80 combinations

It is clear that the drug release from the λ – carrageenan and locust bean gum combination matrices, depends upon the formation of gelatinous swollen mass and its thickness which determines the diffusional path length of the drug to diffuse out from the matrix into dissolution medium. The in vitro drug release profiles of nateglinide from λ – carrageenan and locust bean gum combination matrices (F_{25} – F_{27}) are shown in fig.18. From the fig.18, it can be clearly seen that, as the concentration of total dry polymer decreased in the formulation, the drug release from the matrices goes on decreasing. The drug release from the formulations F_{25} – F_{26} is 88.05% (F_{25}), 97.75% (F_{26}) at t_{24}h and 102.35% (F_{27}) at t_{22}h. As the concentration of total dry polymer decreases in the formulation, the thickness and the viscosity of the gel layer goes on decreasing. This causes to decrease the diffusional path length for the drug to diffuse out from the dry core of the matrix. This might be the reason for the decreased drug release from the matrix formulation. As the formulation F_{26} sustained the drug release upto t_{24}h i.e. 20% (24mg) of polymer concentration of was reduced from the formulation.

Table.No. 40. In vitro drug release profile of F_{25} – F_{27}

Time (hours)	BATCH NO.		
	F25	F26	F27
1	08.31	10.47	16.48
2	13.45	16.17	22.64
4	19.97	21.08	30.47
6	24.63	26.65	39.38
8	30.24	39.14	47.08
10	38.22	48.92	54.22
12	42.38	54.67	61.84
14	50.52	61.07	69.22
16	59.22	69.24	76.54
18	68.54	76.72	81.26
20	74.91	84.24	87.92
22	81.65	91.02	94.24
24	88.05	97.75	102.35

Fig.18. In vitro drug release profile of F_{25} – F_{27}



6.3.4.3. K - carrageenan [Fig. 16, F_3]

Looking at the swelling behavior of the tablets F_3, first the carrageenans swells relatively fast with consequent formation of a gel layer and then swelling slows (fig.19). The responsibility for this behavior is the higher mobility of the water molecules between the polymer chains; they can penetrate more easily because there are fewer sulfate groups, binding water tightly in solvate form at the chains [102]. It was observed that the

within 1h about 200% (axial swelling, fig.20.B) of the initial value and 130% (radial swelling, fig.20.C) of the initial value was reached. As the water uptake of k - carrageenan matrix tablet (F_3) was rapid, the swelling slowed drug release was observed from F_3 from the 1h itself. The gel layer (rubbery state) grows with time as more water permeates into the core of the matrix, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release. When F_3 gets fully hydrated with axial swelling 375% (fig.13.B) and radial swelling 190% (fig.13.C) in 6h, the gel layer slowly dissolved and started eroding away exposing a new gel layer as is commonly observed with swellable matrix tablets.

6.3.4.4. λ – carrageenan [Fig. 16, F_6]

λ – carrageenan is swellable polymer, does not show gelation capability due to high degree of sulfate esterification but it hydrates and swells to a good extent [108]. In case of F_6, it was observed that during dissolution testing of the matrix tablets rapid surface hydration of the matrix F_6 was observed which resulted in its swelling. The extent of swelling determines the diffusional path length for the drug to release from the matrix. It was observed that F_6 swelled rapidly i.e. 196.07% (axial swelling, fig.16.B) of the initial value and 130% (radial swelling, fig.16.C) of the initial value was reached, retarding the drug release from the F_6. As time progresses, the matrix drew more water inside and gets fully hydrated in 6h with axial swelling 416.66% (fig.16.B) and radial swelling of 190%, the glassy core starts diminishing and the tablet dimensions change in the axial and radial directions.

6.3.4.5. Locust bean gum [Fig. 16, F_9]

LBG is a nonionic polysaccharide and the hydration process is independent of pH. When the formulation F_3, is placed in the aqueous medium, liquid penetrates into the tablet and a gel is formed due to uncoiling of the structure of the locust bean gum molecules and the formation of hydrogen bonds with water molecules. As a result, the diameter of the tablet increases progressively and a distinct gel-sol boundary develops. It was observed that F_6 swelled rapidly i.e. 165.09% (axial swelling, fig.19.B) of the initial value and 130% (radial swelling, fig.19.C) of the initial value was reached, which

indicates that the gum hydrated quickly and a sufficient boundary gel formed immediately retarding the drug release from the F_9. This was visually observed during the experiment. As time progresses, the matrix dragged more water inside and gets fully hydrated in 6h with axial swelling 188.67% (fig.19B) and radial swelling of 130%, the glassy core starts diminishing and the tablet dimensions change in the axial and radial directions.

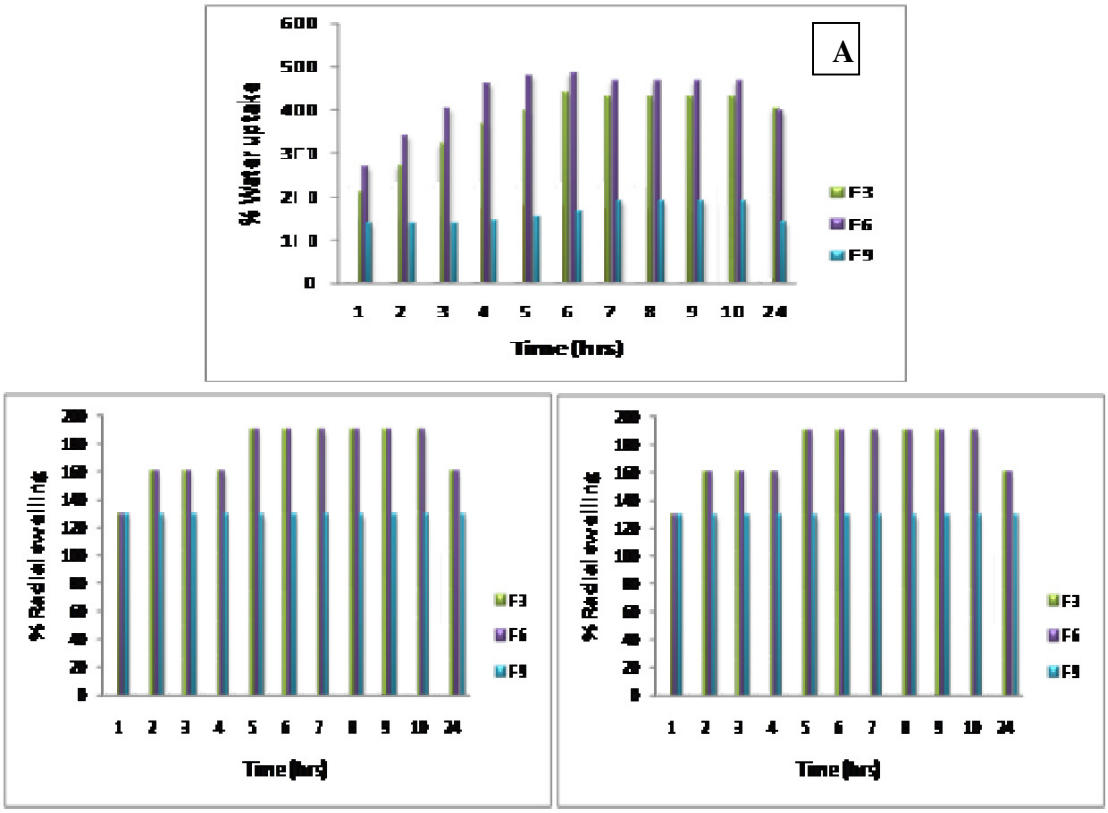


Fig.19. A. Water uptake study of formulations, F_3, F_6 and F_9

B. Axial swelling study of formulations, F_3, F_6 and F_9

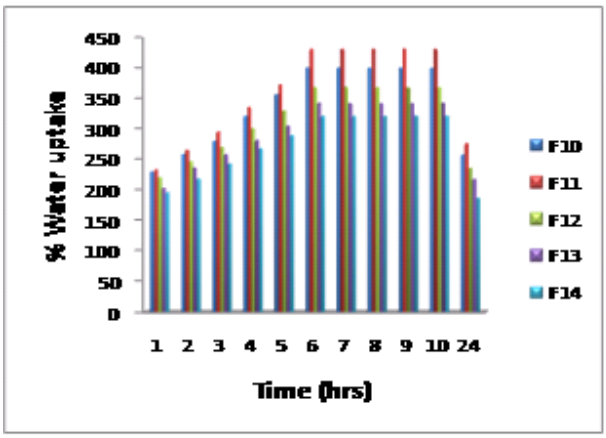
C. Radial swelling study of formulations, F_3, F_6 and F_9

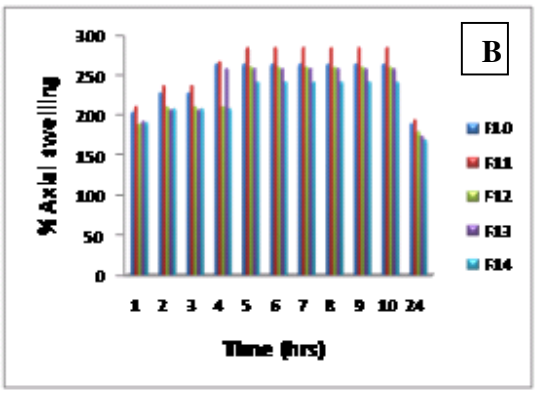
6.3.4.8. K – carrageenan + Locust bean gum

A. K – Carrageenan and locust bean gum combinations

The water uptake and swelling behaviour of the k -carrageenan and locust bean gum combination matrices (F_{10} – F_{14}) were investigated (fig.30) with a gum proportions which are shown in Table 18. As both k -carrageenan and locust bean gum are swellable gel forming polymers, they form highly thick and viscous gel layer increasing the

diffusional path length thus, decreasing the drug release from the matrices. This increased thickness and viscosity of the gel layer also decreases the erosion rate of the matrix tablet. The change in weight is characteristic of the water uptake and swelling which started immediately and continued for 6h (fig.30). The F_{11} showed the maximum drug retardation with maximum water uptake (430.98%) and swelling (axial swelling 285.03% and radial swelling 190%). The k – carrageenan and locust bean gum (40:60) shows the viscous synergism in this ratio. This means that they forms the viscous gel layer more highly thick and viscous gel layer around the matrix tablet than there individual matrices would produce (F_{13} and F_{19}).





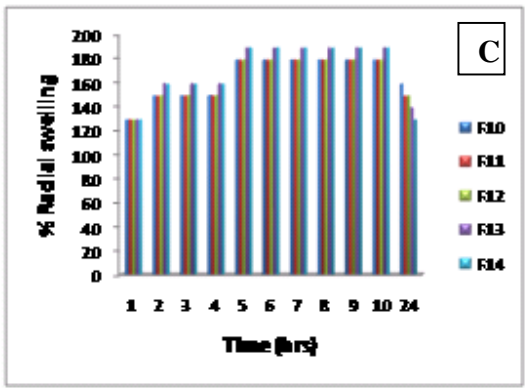


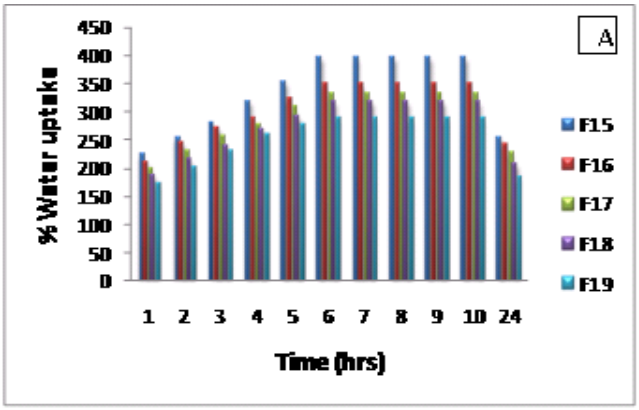
Fig.20. A. Water uptake study of formulations F_{10}, F_{11}, F_{12}, F_{13} and F_{14}

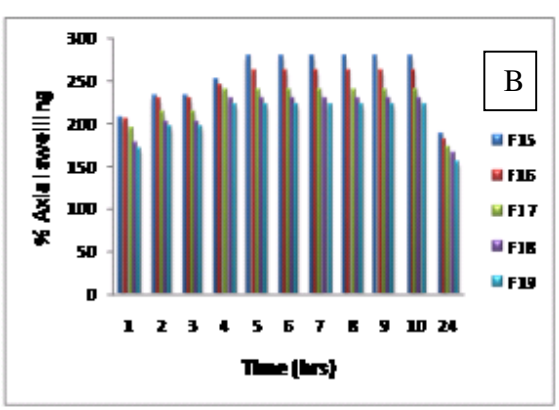
B. Axial swelling study of formulations F_{10}, F_{11}, F_{12}, F_{13} and F_{14}

C. Radial swelling study of formulations F_{10}, F_{11}, F_{12}, F_{13} and F_{14}

B. K – Carrageenan and locust bean gum 40:60 combinations

The water uptake and swelling behaviour were investigated with the formulations mentioned in Table 19. The results water uptake and swelling studies of k - Carrageenan and locust bean gum 40:60 combinations (F_{15} – F_{19}) were shown in fig.31. From the fig.31, it can be concluded that, as the total concentration of polymer decreases in the formulation from F_{15} – F_{19}, the water uptake and swelling of the matrices goes on decreasing. As the total dry polymer concentration decreases in formulation, the lactose concentration in formulation goes on increasing in the formulation from F_{15} – F_{19} (fig.31), the radial and axial dimensions of the matrix diminish along with the reduction in the matrix's weight as the water absorption rate increases. The reason for this increased water uptake due to increased lactose in the formulation has been given in section 6.3.4.7.B. Hence, the drug release from the matrix goes on increasing from F_{15} – F_{19} which can be seen from fig.22. The radial and axial expansion was almost constant after 6 h. This suggests the role of erosion to maintain constant diffusional path length because of proper synchronization between erosion and diffusion. The terminal water uptake and radial/axial swelling of F_{17} was less steep because the diffusional path length and distance to be traveled for dissolution media to reach the dry core increases with time. Hence, the drug release profile of F_{17} fits into the Korsmeyer – Peppas power law equation (anomalous behaviour, n – 0.8026).





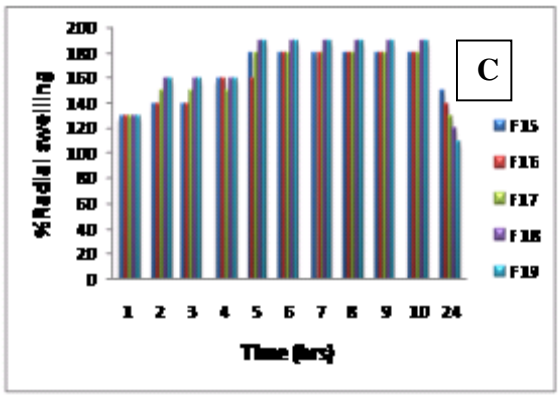


Fig.21. A. Water uptake study of formulations F_{15}, F_{16}, F_{17}, F_{18} and F_{19}

B. Axial swelling study of formulations F_{15},F_{16}, F_{17}, F_{18} and F_{19}

C. Radial swelling study of formulations F_{15}, F_{16}, F_{17}, F_{18} and F_{19}

6.3.4.9. λ – carrageenan + Locust bean gum

A. λ - carrageenan and locust bean gum combinations

The water uptake and swelling behaviour of the λ-carrageenan and locust bean gum combination matrices (F_{10} – F_{14}) were investigated (fig.32) with different gum proportions which are shown in Table 20. λ -carrageenan is not a gel forming polymer, it only swells (hydrates) immediately when it comes in contact with water whereas locust bean gum is swellable gel forming polymer. When both the polymers were combined in a formulation, the erosion rate of the λ –carrageenan also decreases as locust bean gum forms viscous gel layer around the matrix tablet. The thickness and the viscosity of the gel layer determine the extent of drug release from the matrix. As it can be seen from the fig.32, the maximum swelling (axial swelling, 362.54%) and water uptake (402.09%) was

shown by F_{20}, as was the drug release from the matrix. The λ - carrageenan and locust bean gum shows the viscous synergism in 20:80 ratio which suggests that the highly thick and viscous gel layer is formed by F_{20}, which causes the drug release to be retarded maximum.

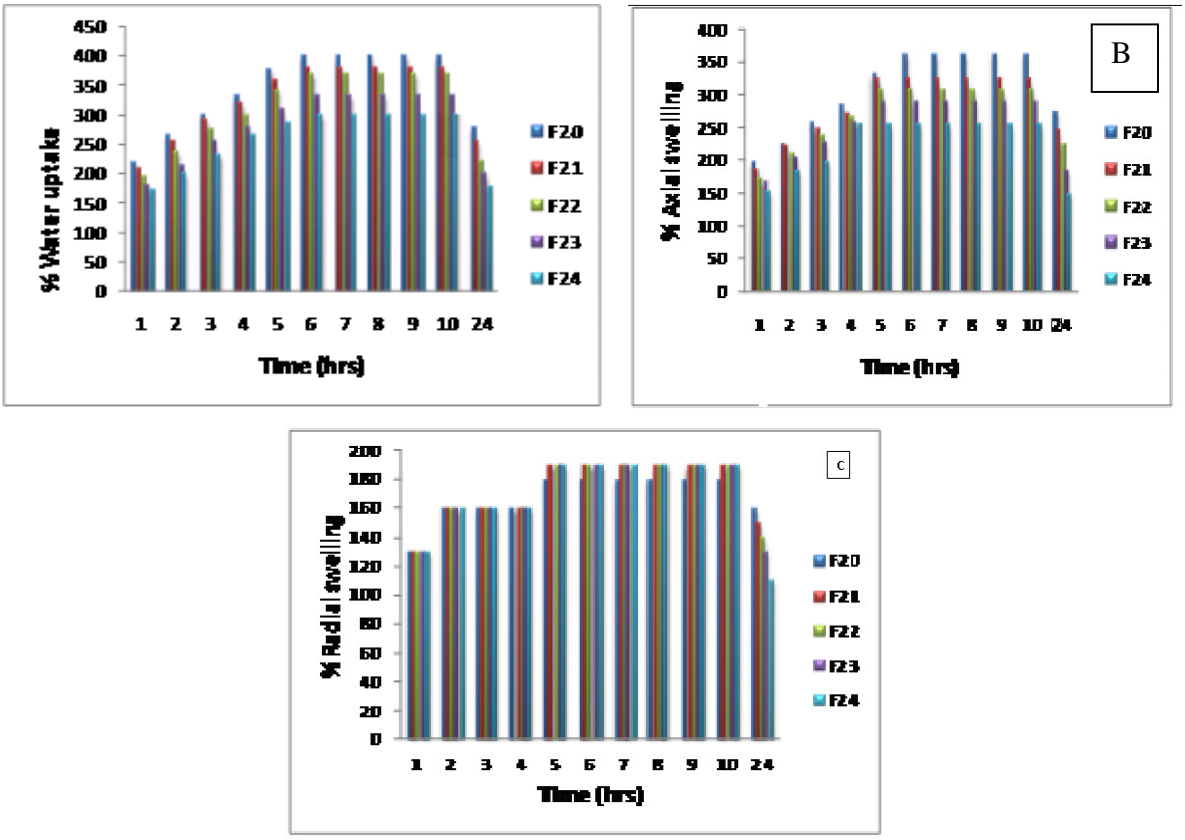


Fig.22.A. Water uptake study of formulations F_{20}, F_{21}, F_{22}, F_{23} and F_{24}

B. Axial swelling study of formulations F_{20}, F_{21}, F_{22}, F_{23} and F_{24}

C. Radial swelling study of formulations F_{20}, F_{21}, F_{22}, F_{23} and F_{24}

B. λ - carrageenan and locust bean gum 20:80 combinations

Measurement of swelling/hydration rates of different matrices were carried out to gain insight into the observed phenomena of drug release with the rates of polymer hydration and to evaluate the extent of water penetration into the tablets. Results of water uptake, axial and radial expansion for F_{25} – F_{27} are shown in fig.33. It is evident that water uptake was continuously rising for 6h until it gets fully hydrated. From the fig.33, it

can be concluded that, as the total concentration of polymer decreases in the formulation from F_{25} – F_{27}, the water uptake and swelling of the matrices goes on decreasing. As the total dry polymer concentration decreases in formulation, the lactose concentration in formulation goes on increasing in the formulation from F_{25} – F_{27} (fig.33), the radial and axial dimensions of the matrix diminish along with the reduction in the matrix's weight as the water absorption rate increases. The reason for this increased water uptake due to increased lactose in the formulation has been given in section 6.3.4.7.B. Hence, the drug release from the matrix goes on increasing from F_{25} – F_{27} which can be seen from the F_{25} – F_{27} (fig.33). The terminal water uptake and radial/axial swelling of F_{26} was less steep because the diffusional path length and distance to be traveled for dissolution media to reach the dry core increases with time. Hence, the drug release profile of F_{26} fits into the Korsmeyer– Peppas power law equation (anomalous behaviour, n – 0.7458)

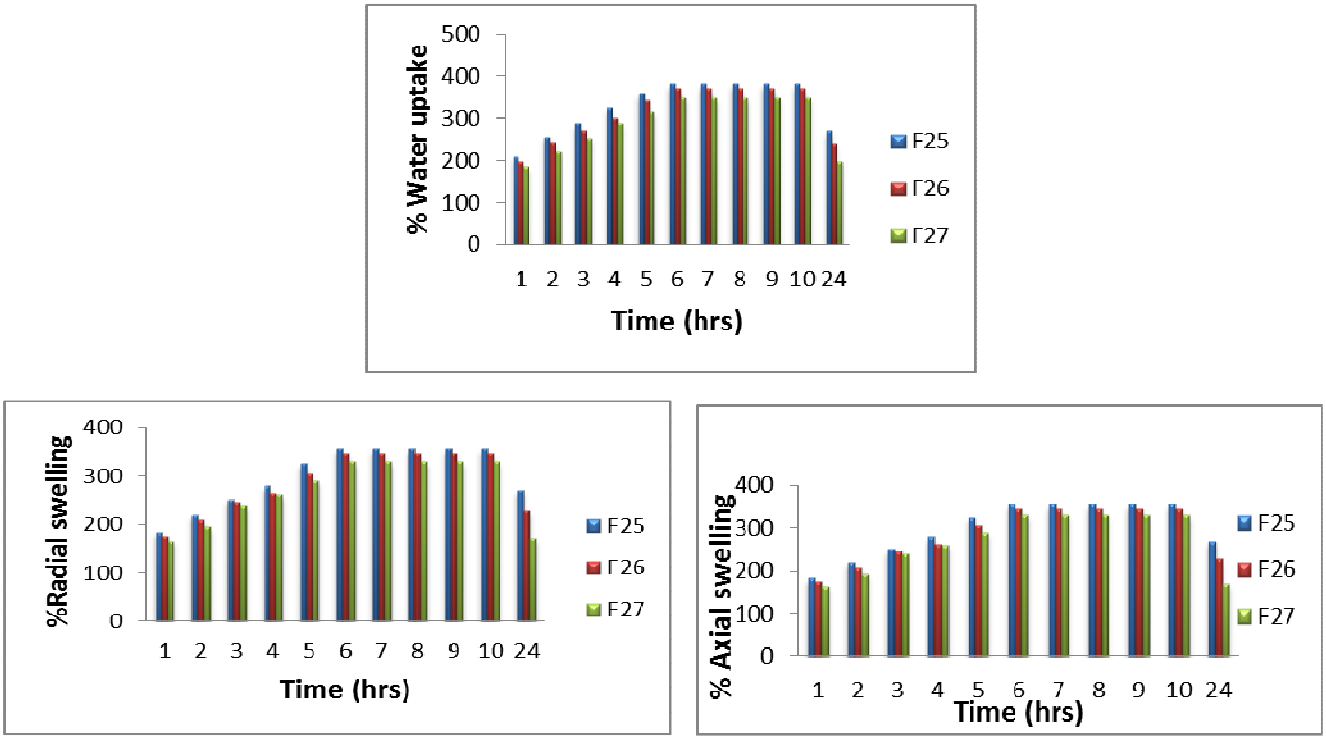


Fig.23. A. Water uptake study of formulations F_{25}, F_{26} and F_{27}
B. Axial swelling study of formulations F_{25}, F_{26} and F_{27}
C. Radial swelling study of formulations F_{25}, F_{26} and F_{27}

12.3 Drug Release Kinetics

The release of nateglinide from the matrices was evaluated by using PCP Disso V3 .To evaluate the drug release kinetics, formulations showing a significant slow release were chosen. In general, the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front", simultaneously, the thickness of the area increases with time in the opposite direction. The mechanism of drug release can be described by a second phenomenon that involves the disentanglement and erosion of the polymer. By using the Korsmeyer and Peppas model equation, the *n* values were obtained between 0.65 and 0.97 for all formulations. These values are characteristic of anomalous kinetics (non Fickian) suggesting that more than one mechanism might be involved in the release kinetics. Here, the polymer relaxation and erosion are the rate-controlling steps. When $n = 0.5$, Fickian diffusion is the rate-controlling step (case I transport). Values of *n* between 0.5 and 1 indicate the contribution of both the diffusion process as well as polymer relaxation in controlling the release kinetics (non-Fickian, anomalous or first-order release). When the exponent *n* takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). It should be noted that the two extreme values of $n = 0.5$ and 1 are only valid for slab geometry. For cylindrical tablets, these values range from $0.45 < n < 0.89$ for Fickian, Anomalous or Case II transport respectively. The Peppas model gave a good fit to most of the dissolution data of the swellable matrix tablets as shown by the R^2values ($0.9892 < R^2 < 0.9968$). For all the nateglinide matrix formulations, the contribution of polymer relaxation occurs throughout the entire dissolution period. This was also apparent from the *n* values obtained for selected formulations, which approach anomalous transport. In general, the relaxational contribution was higher for the formulations with higher *n* values. The k - carrageenan formulation (F_3) showed the highest contribution of polymer relaxation.

Table.41. Drug release parameters for selected formulations

Formulation	n values	R^2	k values	Best fit model
F_{13}	0.9748	0.9897	4.2354	Peppas
F_{16}	0.9448	0.9897	4.2416	Peppas
F_{19}	0.7997	0.9935	4.1579	Peppas
F_{17}	0.8026	0.9968	4.1625	Peppas
F_{26}	0.7458	0.9914	4.1145	Peppas

The regression coefficient values and n values show that the drug releases follow Non - Fickian release (Diffusion and swelling).

13. SUMMARY

Nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] is a novel, highly physiologic, mealtime glucose regulator approved for the treatment of type II diabetes mellitus. Nateglinide is a BCS class II (Insoluble, highly permeable) drug. The plasma half life of nateglinide is 1.5h and bioavailability of 73%. The usual oral dosage regimen is 60— 180mg taken 3 times a day for nateglinide immediate release tablets. The controlled or sustained release formulation of nateglinide would be more useful than the nateglinide immediate release tablets from the view point of avoidance of side effect, improvement of compliance to patients and to enable control of both post prandial blood glucose level and fasting blood glucose level for moderate and severe diabetes patients. Hence, an attempt was made to develop a sustained-release (SR) oral dosage form of nateglinide instead of IR tablet.

The present work studied the natural polymer based once a day matrix tablet of nateglinide. From the wide range of hydrophilic polymers, k – carrageenan, λ – carrageenan and locust bean gum. Combinations of the two different gums k-carrageenan and locust bean gum and λ-carrageenan and locust bean gum were formulated in different ratios 20:80, 40:60, 50:50, 60:40 and 80:20 to exploit rheological synergism between two gums. Further the formulations were prepared dorm the formulation which exhibited maximum retardation such that each contains 10% less polymer concentration than the previous formulation in order to achieve the once a day matrix tablet of nateglinide containing least amount of polymer. The blends were prepared by non-aqueous wet granulation techniques with lactose as a diluent in formulations. The dried blends were compressed with other necessary excipients. The tablets were evaluated for hardness, thickness, drug content uniformity, in-vitro drug release studies for 24 hours (USP dissolution apparatus II, phosphate buffer-pH 6.8, 50 rpm, 37±0.5ºC), water uptake studies, swelling studies and in of the matrix tablet. The amount of Nateglinide released from the tablet formulations was estimated at 210nm using a UV spectrophotometer. The kinetic analysis of selected formulations were performed and found to follow Korsmeyer-Peppas model through non-fickian transport mechanism.

The following conclusions can be drawn from the above study.

From the results obtained we can conclude that the polymers selected for the study, can be used individually for the sustained drug delivery of nateglinide locust bean gum was used in combination with k-carrageenan and λ-carrageenan in 60:40 and 20:80 ratios respectively with least in vitro drug release and can be used to reduce the concentration of polymer from the tablet.30% polymer reduction in case of k-carrageenan and locust bean gum and 20% with λ-carrageenan and locust bean gum combination was achieved.

14. CONCLUSION

Once a day sustained release matrix tablets of nateglinide was prepared by using natural polymers k-carrageenan,lambda carrageenan and locust bean gum. Natural polymers were selected due to their easy availability and cheaper in coast and we can get standard uniformity and combinations of two different gums carrageenan and locust been gum were formulated in different ratios to exploit the rheological synergism between two gums in order to achive once a day matrix tablets of nateglinide further formulations were prepared from the formulations exhibited maximum retardation the controlled or sustained release formulations of nateglinide would be more useful than the nateglinide immediate release tablets from the new point of side effects improvement of compliance to patients and to enable to control of both post prandial blood glucose level and fasting blood glucose level for moderate and sever diabates patients.

Hence an attempt was made to develop a sustained release oral dosage form of nateglinide instead of immediate release tablet.

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