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# FORMULATION AND DEVELOPMENT OF REPAGLINIDE MICROPARTICLES BY IONOTROPIC GELATION TECHNIQUE

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**Keywords**:
Microparticles, Repaglinide, Ionotropic Gelation Technique.

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**ABSTRACT:**
The present investigation involves formulation and evaluation of microparticles with repaglinide as model drug for prolongation of drug release time. An attempt was made to prepare microparticles of repaglinide by ionotropic gelation technique, with a view to deliver the drug at sustained or controlled manner in gastrointestinal tract and consequently into systemic circulation. The microparticles were formulated by calcium chloride cross-linking method using various concentration of Hydroxy Propyl Methyl Cellulose and Chitosan by dropping the Drug-Polymer solution along with sodium alginate in calcium chloride solution.
The prepared microparticles were evaluated for Flow behavior, Compatibility study, Drug Entrapment Efficiency, In-vitro Dissolution, Scanning Electron Microscopy and Sieving method. Among the seven formulations prepared and evaluated F1 and F4 are found to show satisfactory results. The Prepared
Microparticles shows entrapment efficiency of 78.62% to 91.25% Fourier transform Infrared spectroscopy confirmed the absence of any Drug-Polymer interaction. In-vitro release studies carried out in 1.2 pH and 7.2 pH phosphate buffer solution shows 93.78% and 91.78% of drug was released from F1 and F4 respectively. The
results of Flow behavior and Particle size analysis were found to be in the official limits. The In-vitro release studies shows that formulation F1, F2 and F3 releases 91.99 %, 81.66 % and 71.66 % respectively after 12 hours. Formulation F4, F5 and F6 shows release of 92.11%, 81.93% and 81.76% respectively. Formulation F7 which is a combination of hydroxy propyl methyl cellulose and Chitosan shows drug release of 71.88%.

**Introduction:**

In the last decade, significant effort was taken to develop nanoparticles, drug delivery (Fessi et al., 1992; Galindo-Rodriguez et al., 2004; Oppenheim, 1981; Alonso, 1996; Bigger et al., 2002). Nanoparticles are submicron sized colloidal polymeric systems. The micro/nanoparticulate drug delivery systems offer numerous advantages over the conventional dosage forms. These include improved efficacy, reduced toxicity and improved patient compliance (Soppimath et al., 2001; Kreuter, 1994; Brannon-Peppas, 1995; Couvreur et al., 1986). Compared to the traditional micron-sized supports used in separation process, nanosized carriers possess quite good performance due to high specific surface area and the absence of internal diffusion resistance (Chang et al., 2006). In particular, micropartices are able to protect drugs from degradation, to improve permeation/penetration of the drugs across mucosal surfaces and also to control the release of the encapsulated or adsorbed drug (Florence et al., 1995; Takeuchi et al., 2001).

Microtechnology is now frequently used for various applications in fiber and textiles (Perelshtein et al., 2008), agriculture (Speiser, 2008; Lai et al., 2006), electronics (Huang et al., 2003), forensic science (Choi et al., 2008), space (Liu et al., 2007) and medical therapeutics (Bender et al., 1996;

Bonduelle and Foucher, 1992; ahanshahi and Babaei, 2008; Kawashima et al., 2000; Rieux et al., 2006).These nanoparticle drug formulation reduces the patient expenses and risks of toxicity (Glen, 2005). Polymeric nanoparticles have been synthesized using various methods (Reis et al., 2006) according to needs of its application and type of drugs to been capsulated. These microparticles are extensively used for the microencapsulation of various useful bioactive molecules and medicinal drugs to develop nanomedicine (Panyam and Labhasetwar, 2003). These micromedicines have many advantages in the protection of premature degradation and interaction with the biological environment, enhancement of absorption into a selected tissue, bioavailability, retention time and improvement of intracellular penetration (Alexis et al., 2008).

However, microparticle are highly preferred and frequently used to improve the therapeutic value of various water soluble/ insoluble medicinal drugs and bioactive molecules by improving bioavailability, solubility and retention time (Shenoy and Amiji,2005). Such microparticles show promise in drug delivery system and provide controlled/sustained release property, sub cellular size and biocompatibility with tissue and cells (Panyam and Labhasetwa, 2003).

Among the various polymers used for the development of sustained release formulations, one of the most widely used polysaccharides for different pharmaceutical purposes is chitosan and its derivatives (Thanou et al., 2001; Morishita and Peppas, 2006; Wilson et al., 2009). Chitosan is a natural cationic polysaccharide derived by deacetylation of chitin, a copolymer consisting of combined units of glucosamine and N-acetyl glucosamine (Lee et al., 1997; Majeti, 2000). In the pharmaceutical field chitosan's advantageous biological properties have prompted its extensive study as a carrier both of drugs (Bayomi et al., 1998; Mi et al., 2001) and of proteins (Calvo et al., 1997). This cationic polymer has attracted a great deal of attention as a drug delivery carrier because of its unique properties, such as acceptable biocompatibility (De Campos et al., 2001), low toxicity (Illum et al., 2001) and the ability to enhance the absorption of hydrophilic molecules across the epithelium via the paracellular transport pathway (Schipper et al., 1999). In the drug delivery field, the vesicles based on chitosan and derivatives can be used for transdermal, nasal, ocular, oral and parenteral administration and other application (Thanou et al., 2001; Thein-Han and Stevens, 2004).

Diabetes mellitus is a major and growing public health problem throughout the world, with estimated world wide prevalence in 2000 of 150 million people, expected to increase to 220 million people by 2010. Recent estimates project that the number of patient's diaganosed with type II diabetes will more than double to 300 million before 2025 (Nagappa, 2008). Diabetes Mellitus (DM) is defined as a group of metabolic diseases the common feature of which is an elevated blood glucose level (hyperglycaemia). Chronic hyperglycaemia is associated with the long-term consequences of diabetes that include damage and dysfunction of the cardiovascular system, eyes, kidneys and nerves. The complications of diabetes are often divided into two groups: microvascular

(retinopathy, nephropathy and neuropathy) and macrovascular (ischaemic heart disease, stroke, peripheral vascular disease). Together, these make diabetes the seventh most common cause of death in the developed world (McGinity and O'Donnell, 1997). Hence, we have focused the attention on anti diabetic treatments.

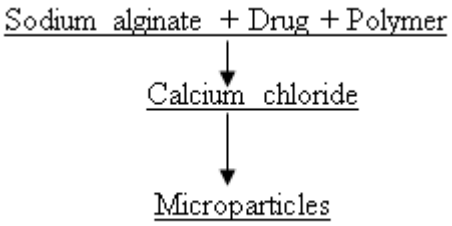
Repaglinide (Rg), a fast and short acting meglitinide analog with a very short half-life (1 h) and low bioavailability (50%) (Jain et al., 2005) was chosen as the drug to overcome the problem due to the conventional dosage form. In the present study, an attempt has been made to formulate Repaglinide-loaded CN nanoparticles, which may provide prolonged drug delivery in the treatment of diabetic disorders and decreases the related side- effects.

## MATERIALS AND METHODS

Materials: The research project was performed at Veeryatan college of pharmaceutical siences, khutch , bhuj, gujarat. Repaglinide (Rg) was received from Sun Pharmaceuticals Ltd., Mumbai. . Hydroxy Propyl Methyl Cellulose K4 M was gifted from JBCPL, Panoli, Gujarat. Chitosan was received from JBCPL, Panoli, Gujarat. Sodium Alginate was gifted from S. D. Fine Chem. Ltd. Mumbai. Calcium Chloride was gifted from S. D. Fine Chem. Ltd. Mumbai. And acetone from (Ranbaxy Fine chemicals Ltd, New Delhi), and all other chemicals used were of analytical grade.

### Preparation of polymeric nanoparticles:

In the present study, microparticles of Repaglinide were prepared by ionotropic gelation technique. In this method weighed quantity of Repaglinide was added to 50 ml sodium alginate solution and thoroughly mixed with a stirrer at 500 rpm. For the formation of microparticles, 50 ml of this solution was extruded dropwise from a needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the 0 obtained microparticles were washed with water and dried at 70 C for 2 hrs in an oven. Three sets of microparticles were prepared. In the first set microparticles of repaglinide were prepared using only hydroxyl propyl methyl cellulose in different concentrations. In the second set, microparticles of the drug were prepared by using only chitosan in different concentrations. In the third set, microparticles of the drug were prepared in a combination of polymers like hydroxyl propyl methyl cellulose and chitosan.




### Nanoparticle recovery:

The microparticle (MP) recovery, which is also referred to as microparticle yield in the literature, calculated using Eq.1. The individual values were determined (Govender et al., 1999).

$$\text{Eq. (1)} \quad \text{Microparticles recovery (\%)} = \frac{\text{Mass of microparticles recovered}}{\text{Mass of polymeric microparticles, drug and any formulation excipient used in formulation}} \times 100$$

### Determination of drug incorporation efficiency:

Drug entrapment efficiency of repaglinide was performed by accurately weighing 100 mg of microparticles and suspended in 100 ml of simulated intestinal fluid of pH 7.2 ± 0.1 and it was kept for 24 hrs. Next day it was stirred for 15 mins, and subjected for filtration. After suitable dilution, Repaglinide content in the filtrate was analyzed spectrophotometrically at 247 nm using Shimadzu 1201 UV-visible spectrophotometer. The absorbance found from the UV-spectrophotometer was plotted on the standard curve to get the concentration of the entrapped drug. Calculating this concentration with the dilution factor we get the percentage drug encapsulated in microparticles.

$$\text{Eq. (2)} \quad \text{Encapsulation efficiency (\%)} = \frac{\text{Actual amount of drug in nanoparticles}}{\text{Theoretical amount of drug}} \times 100$$

$$\text{Eq. (3)} \quad \text{Loading efficiency (\%)} = \frac{\text{Amount of drug in nanoparticles}}{\text{Total amount of nanoparticles}} \times 100$$

Particle size determination

49, 50

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The particle size of a pharmaceutical substance is strictly maintained in order to get optimal biological activity. Methods to estimate particle size are :

a. Optical Microscopy

b. Sieving Method
c. Sedimentation Method
d. Elutriation Method
e. Centrifugal defractometry
f. Permeability Method
g. Light scattering Method

Sieving Method:

Standard sieves of different mesh numbers are available commercially as per the specifications of IP and USP. Sieves are arranged in a nest with the coarsest at the top. A sample (50gms) of the powder is placed on the top sieves. This sieve set is fixed to the mechanical shaker apparatus and shaken for a certain period of time (20 minutes). The powder retained on each sieve is weighed. Frequently, the powder is assigned the mesh number of the screen through which it passes or on which it is retained. It is expressed in terms of arithmetic or geometric mean of the two sieves.

Scanning electron microscopy:

Morphology details of the specimens were determined by using a scanning electron microscope (SEM), Model JSM 35CF, JEOL, Japan. The samples were dried thoroughly in vacuum desicator before mounting on brass specimen studies. The samples were mounted on specimen studies using double sided adhesive tape, and gold- palladium alloy of 120Ao kness was coated on the sample using sputter coating unit (Model E5 100 Polaron U.K.) in an Argon ambient of 8-10 pascal with plasma voltage about 20 MA. The sputtering was done for nearly 3 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage of about 15 KV with load current of about 80 MA. The condenser lens position was maintained between 4.4--5.1. The objectives lens aperture has a diameter of 240 microns and the working distance WD = 39 mm52, 53.

Fourier transform infrared spectroscopy:

Infrared spectroscopy was conducted using a Avatar 320-FT IR spectrophotometer and the spectrum was recorded in the region of 4000-400 cm-1. The procedure consist of dispersing a sample (drug, polymer and Rg-CN nanoparticle preparation) in potassium bromide pellet (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

In-vitro Dissolution Studies :

In-vitro release profile of the microparticles was evaluated using rotating basket dissolution apparatus. 900 ml of acid buffer (pH1.2), and phosphate buffer (pH 7.2) maintained at 37±0.5 0C were used as dissolution medias respectively, and the basket was rotated at a constant speed of 50 rpm. Accurately weighed amount of microparticles equivalent to 200 mg of drug were placed in the baskets. Aliquotes of samples were withdrawn at the interval of 1 hour for pH 1.2 and 2 hrs for 7.2 pH. The samples withdrawn were filtered, diluted suitably and analyzed at 247 nm spectrophotometrically for drug release51.

Kinetics of drug release

In order to analyze the drug release mechanism, in vitro release data were fitted into a zero-order (57), first order

(58-60), Higuchi (61-63), Hixon-Crowell cube root law (64), Korsmeyer-peppas model (65-68).

The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration.

$C = k_o t$ (Equation 11.1)

Where C is the concentration of the drug at time (t) and ko is the zero-order release rate constant.

The first order Equation (Equation 11.2) describes the release from a system where the release rate is concentration dependent.

$\log C = \log C0 - kt / 2.303$ (Equation 11.2)

Higuchi described the release of drugs from porous, insoluble matrix as a square root of time dependent process based on Fickian diffusion as shown in Equation 11.3.

$Q = Kt^{1/2}$ (Equation 11.3)

The Hixson-Crowell cube root law Equation 11.4 describes the release from systems where there is a change in surface area and diameter of particles.

$Q0^{1/3} - Qt^{1/3} = KHC\,t$ (Equation 11.4)

To evaluate the mechanism of drug release, data for the first 60% of drug release were plotted into the Korsmeyer et al's equation (Equation 11.5) as log cumulative percentage of drug released vs log time, and the exponent (n) was calculated using the slope of the straight line.

$$Mt/Mo = Ktn \qquad \text{(Equation 11.5)}$$

where (Mt/Mo) is the fractional solute release, (t) is the release time, (K) is a kinetic constant characteristic of the drug/polymer system, and (n) is an exponent that characterizes the mechanism of release of tracers [61]. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release [62].

**Stability study**

The selected formulations were subjected to accelerated stability studies to evaluate effect of stress conditions according to ICH guidelines. Formulations were packed in glass vials sealed with aluminum foil and rubber cap and subjected to elevated temperature and humidity conditions of 40 ± 2 °C/75 ± 5% RH, 30 ± 2 °C/ 65 ± 5% RH and also 25 ± 2 °C/60 ± 5% RH. Samples were withdrawn at the end of 1, 3 and 6 months and evaluated for physical properties, drug content and in vitro drug release [350].

**RESULTS AND DISCUSSION**

**Formation of microparticles:**

In the present study, microparticles of Repaglinide were prepared by ionotropic gelation technique with three different ratios of three different polymers as shown in table 1. In this method weighed quantity of Repaglinide was added to 50 ml sodium alginate solution and thoroughly mixed with a stirrer at 500 rpm. For the formation of microparticles, 50 ml of this solution was extruded dropwise from a needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microparticles were washed with water and dried at 70° C for 2 hrs in an oven. Three sets of microparticles were prepared. In the first set microparticles of repaglinide were prepared using only hydroxyl propyl methyl cellulose in different concentrations. In the second set, microparticles of the drug were prepared by using only chitosan in different concentrations. In the third set, microparticles of the drug were prepared in a combination of polymers like hydroxyl propyl methyl cellulose and chitosan.

**Effect of drug entrapment:**

The percentage entrapment efficiency was varied by varying the characteristics of polymer and cross linking agent. Normally the low entrapment efficiency was due to high affinity of drug and polymer in different solvents (drug in organic solvent and polymer in aqueous solvent and vice-versa) during the nanoparticle preparation and the drug loading content and entrapment efficiency were mainly affected by the polymer ratios. Peng et al. (2007) also reported that the improved encapsulation efficiency may be due to the greater proportion of polymer with respect to the amount of drug. In our Rg-CN nanoparticle preparation, the drug and the polymer were dissolved in organic phase and greater proportion of polymer were added to the drug. Hence, there was no chance in the diffusion of drug away from the polymer. The percentage drug entrapment of Repaglinide in the formulations was found to be good at all levels of drug loading. The high entrapment efficiency of Repaglinide is believed to be due to its poor aqueous solubility, high affinity of drug and polymer in the same solvent (organic solvent) and increased polymer ratio. Present report was found to be similar to that of early findings (Jain et al., 2005).

The researchers (Nuwa et al., 1994) attributed the decreased drug entrapment with increasing theoretical drug loadings to an enhanced drug leakage into the aqueous phase (if drug is water soluble) or into the organic phase (if drug is water insoluble) at high loadings. This would also lead to an enhanced drug loss. Compared to 1:1, 1:1.5 ratios the 1:2 ratio shown high drug content and it produced an enhanced drug leakage which influences the absolute release profiles and responsible for an increased initial burst. Avinash et al. (2007) have reported that increase in drug content in the particles influences the absolute release profiles such as the cumulative amount of drug released at any time and the induction period increases. The increase in drug content increased the amount of drug close to the surface which is responsible for an increased initial burst.

The increase in drug in the core of nanoparticles is responsible for a prolonged drug release from the polymer. In the Rg-CN nanoparticles preparation, according to the result of efficiency of recovery and drug entrapment of nanoparticles among the three different ratios, 1:2 ratio was selected as the best ratio compare to 1:1.5 and 1:1 because these ratios leads to a low drug entrapment which implied high drug wastage during the preparation and 1:2 ratio shown low drug wastage. These polymeric nanoparticles were prepared at three consecutive times for reproducibility and The drug entrapment efficiency of all the formulations were in the range between 78.62 % to 91.25 %. The results of drug entrapment efficiency are shown in Table No.2. Drug entrapment efficiency of microparticles increases with increase in concentration of HPMC and chitosan. Douglas et al. (1987) have reported that high nanoparticle recovery is required for reducing manufacturing costs and its size and morphology important for quality control and bio distribution.

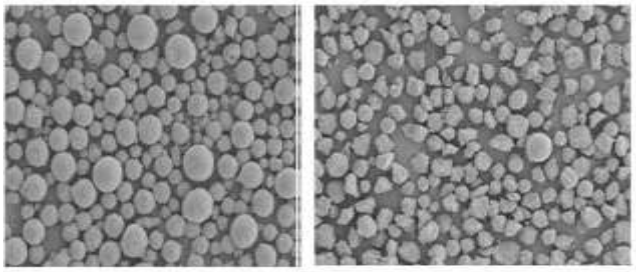
**Morphology of microparticles**

Morphology of the microparticles were investigated by Scanning electron microscopy. The photographs of formulations taken by scanning electron microscope are shown in the figure No.1 and 2. Microparticles of formulation F1 were approximately spherical and their surface was rough giving them a sandy appearance. The surface characteristics observed for Formulation F4 shows oval or slightly spherical structure with smooth appearance. From the photographic observation it can be stated that bridging and dense nature of formulation indicated to retard the release of Repaglinide.

| Formulation No. | Sodium Alginate (W/V) | Calcium Chloride (W/V) | HPMC (W/V) | Chitosan (W/V) | Drug (Repaglinide) in mg |
|---|---|---|---|---|---|
| $F_1$ | 2% | 4% | 1% | --- | 8 mg |
| $F_2$ | 2% | 4% | 1.5% | --- | 8 mg |
| $F_3$ | 2% | 4% | 2% | --- | 8 mg |
| $F_4$ | 2% | 4% | --- | 1% | 8 mg |
| $F_5$ | 2% | 4% | --- | 1.5% | 8 mg |
| $F_6$ | 2% | 4% | --- | 2% | 8 mg |
| $F_7$ | 2% | 4% | 1% | 1% | 8 mg |

| Formulations | Absorbance at 247nm | Theoretical content (mg) | Actual content (mg) | % Drug Entrapment Efficiency |
|---|---|---|---|---|
| $F_1$ | 0.0521 | 8 | 6.29 | 78.62 |
| $F_2$ | 0.0569 | 8 | 6.87 | 85.87 |
| $F_3$ | 0.0601 | 8 | 7.26 | 90.75 |
| $F_4$ | 0.0549 | 8 | 6.63 | 80.15 |
| $F_5$ | 0.0591 | 8 | 7.14 | 86.35 |
| $F_6$ | 0.0604 | 8 | 7.30 | 91.25 |
| $F_7$ | 0.0537 | 8 | 6.49 | 81.12 |

**Figure 1& 2: SEM of Formulation F1 and F2 Under Low Magnification**



**FT-Infrared Spectroscopy (FTIR):**

To check the compatibility of the drug with various polymers, IR spectra of drugs, polymers and combination of the drug and polymers were taken. The IR spectra of the drug, polymers and their combinations are shown in Spectra No.1.

The characteristics absorption peaks of repaglinide were obtained at1687.3cm-1, 2935.03 cm-1, 1217.12 cm-1, and 3308.38cm-1. The IR spectras of the drug and polymer combinations were compared with the spectra of pure drug and individual polymers. The principle peaks obtained for the combinations were almost similar to that of the drug. The details of IR spectra are mentioned in Table No.3. The IR spectra of the Drug-HPMC, Drug – chitosan, and Drug-Sodium alginate, did not show any changes. The possibility of interaction was ruled out as there was no major shift in the absorption bands of drug and the formulations as shown in Spectra No.1

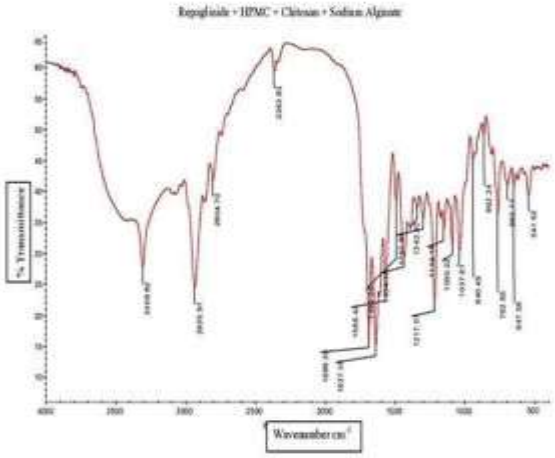


**Figure 3**: FTIR of Repaglinide + HPMC + Chitosan + Sodium Alginate microparticle

**In-vitro Dissolution Studies:**

Dissolution studies of all the formulations were carried out using dissolution tester USP XXIIII. The dissolution studies were conducted by using two different dissolution medias, pH 1.2 and pH 7.2.

The data obtained in the in-vitro dissolution studies were grouped according to modes of data treatment as follows: -

Cumulative percent drug release V/s. Time (Zero-order).

Cumulative percent drug retained V/s. Square root of Time (Higuchi Matrix Model).

Log Cumulative percent drug retained V/s. Time (First-order).

Cumulative percent drug release in (mg) V/s. Time (Krosmeyer-Peppas Model).

The results of the in-vitro dissolution studies of formulations F1 to F7 are shown in table 14 to 20. The plots of Cumulative percentage drug release V/s. Time, Cumulative percent drug retained V/s. Time, Log Cumulative percent drug retained V/s. Time and Cumulative percent drug release in (mg) V/s. Time were drawn and represented graphically as shown in Graph No. 4 to 15, respectively.

The formulation F1, F2 and F3 Containing 1%, 1.5%, and 2% Hydroxy Propyl Methyl Cellulose respectively showed a release of 91.99%, 81.66% and 71.66% after 12 hours. This shows that more sustained release was observed with the increase in percentage of Hydroxy Propyl Methyl Cellulose. The formulation F4, F5 and F6 Containing 1%, 1.5%, and 2% Chitosan respectively showed a release of 92.11%, 81.93% and 81.79% after 12 hours. This shows that more sustained release was observed with the increase in percentage of Chitosan. The formulation F7 containing both 1% HPMC and 1% chitosan showed a release of 71.88%. This shows that the particles formulated with HPMC and Chitosan prolongs the release but without satisfactory surface characteristics.

The formulations F1, F2 and F3 containing 1%, 1.5%, and 2% Hydroxy Propyl Methyl Cellulose respectively showed a release that more sustained release was observed with the increase in percentage of HPMC after 12 hours. This indicates that the release rate is further retarded due to addition and in percentage of Hydroxy Propyl Methyl Cellulose because of the strong bonds between the HPMC and sodium alginate. As the percentage of HPMC increased the release was further sustained.

The formulations F4, F5 and F6 containing 1%, 1.5%, and 2% chitosan respectively showed a release that more sustained release was observed with the increase in percentage of Chitosan after 12 hours. This indicates that the release rate is further retarded due to addition and in percentage of chitosan because of the strong bonds between the chitosan and sodium alginate. As the percentage of chitosan increased the release was further sustained.

**In vitro release kinetics study:**

Further these drug releases were subjected for mathematical treatment to check weather the release is following first order or zero-order kinetics. The co-efficient of correlation values are shown in table No.3. The values of co-efficient of correlation were found to be best fitted to Krosmeyer-Peppas model and Higuchi model. The calculated values of various kinetic models are shown in table No. 4 The values of diffusion co-efficient (n) for formulations F1 to F7 are shown to be 0.453, 0.499, 0.547, 0.418, 0.515, 0.469, 0.596 respectively which indicates that the release of drug occurs by diffusion following Fickian transport and Anomalous mechanism.

**Table 3: Values of Correlation-coefficient (r) of Repaglinide**

| Formulations | Zero Order | First Order |
|---|---|---|
| F1 | 0.9757 | 0.8576 |
| F2 | 0.9202 | 0.9835 |
| F3 | 0.9566 | 0.9835 |
| F4 | 0.9884 | 0.9473 |
| F5 | 0.7267 | 0.9345 |
| F6 | 0.9648 | 0.981 |
| F7 | 0.8167 | 0.9811 |

**Table 4: Curve Fitting Data of the Release Profile for Repaglinide**

| Formulations | Matrix | Krosmeyer- Peppas | n-values | Mechanism |
|---|---|---|---|---|
| F1 | 0.9521 | 0.9841 | 0.453 | Fickian |
| F2 | 0.9768 | 0.9575 | 0.499 | Fickian |
| F3 | 0.9702 | 0.9878 | 0.547 | Anomalous |
| F4 | 0.9326 | 0.9912 | 0.418 | Fickian |
| F5 | 0.9636 | 0.8575 | 0.515 | Anomalous |
| F6 | 0.9563 | 0.9750 | 0.469 | Fickian |
| F7 | 0.9943 | 0.9267 | 0.596 | Anomalous |

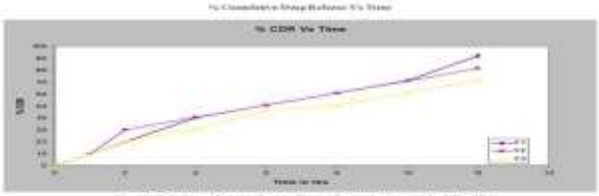



**Fig 4**: In vitro drug release from formulation F1, F2, F3

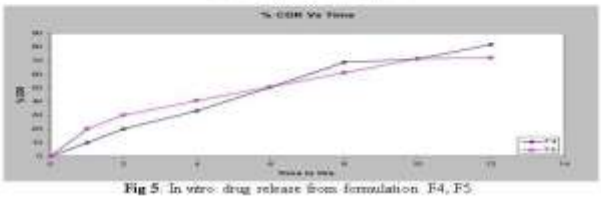



**Fig 5**: In vitro drug release from formulation F4, F5

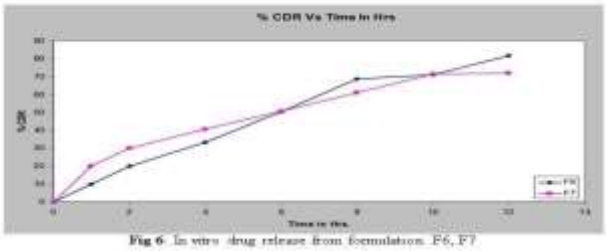



**Fig 6**: In vitro drug release from formulation F6, F7

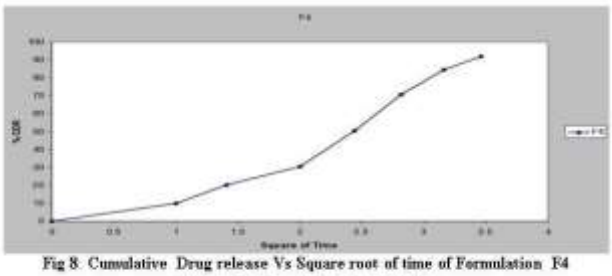


Fig 8: Cumulative Drug release Vs Square root of time of Formulation F4

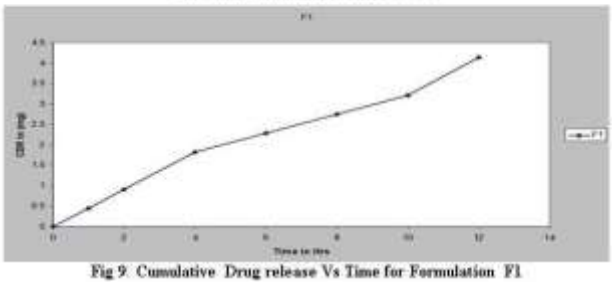


Fig 9: Cumulative Drug release Vs Time for Formulation F1

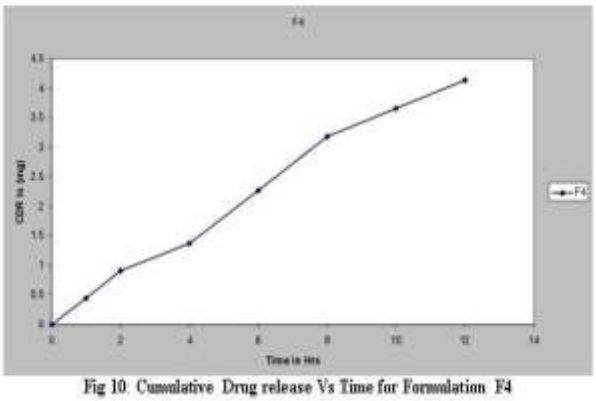


Fig 10: Cumulative Drug release Vs Time for Formulation F4

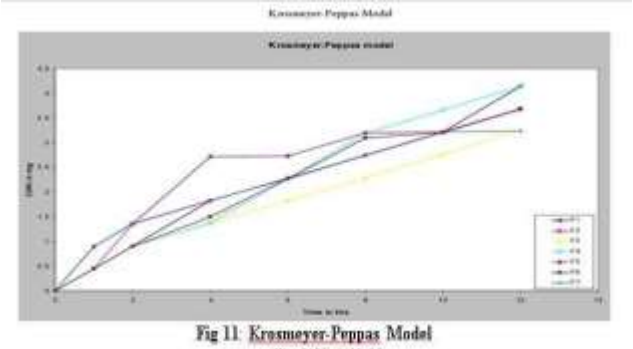


Fig 11: Krosmeyer-Peppas Model

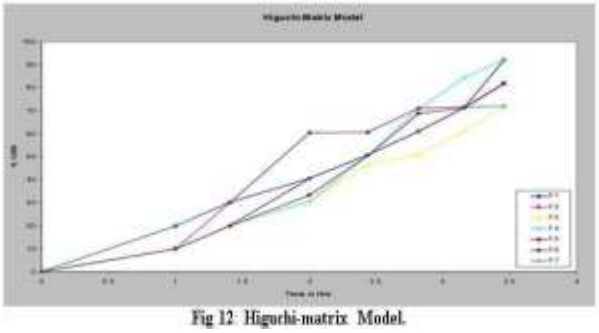


Fig 12: Higuchi-matrix Model.

## CONCLUSION

From the above experimental results it can be concluded that:-

- Oral controlled release of Repaglinide can be achieved by ionotropic gelation technique using HPMC and Chitosan as a polymer.
- The IR spectras revealed that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug.
- Prepared microparticles exhibited Krosmeyer-Peppas kinetics/Higuchi model and the release profile was by Fickian and Anomalous.
- From the study it is evident that a promising controlled release microparticulate drug delivery of Repaglinide can be developed. Further in-vivo investigation is required to establish efficacy of these formulations.
- The study also indicated that the amount of drug release decreases with an increase in the polymer concentration.
- Microparticles formulated with a combination of HPMC and Chitosan prolonged the release but gave unsatisfactory kinetic results with low correlation coefficient values.

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