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FORMULATION AND EVALUATION OF MICROPARTICULATE SYSTEM FOR CONTROLLED DELIVERY OF NATEGLINIDE BY IONOTROPIC GELATION METHOD

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ABSTRACT

Controlled Release oral product namely microspheres for Nateglinide prepared by Ionotropic Gelation Technique to overcome the drug related adverse effects like gastric irritation, improve its bioavailability in different gastrointestinal pH conditions. Total twenty four formulation batches were formulated using sodium alginate alone and combination with Carbopol, HPMC and Chitosan as drug release modifiers in various proportions and investigate for physiochemical and drug release properties. All investigated properties showed satisfactory results. While increase in the concentration of sodium alginate and other polymer dispersions increased sphericity, size distribution, flow properties and mean diameter of the microspheres. The drug entrapment efficiency of microparticles was found to ≥ 86%. Increase in the concentration of concentration of other hydrophilic polymers such as Carbopol and HPMC in the alginate gel matrix retarded (≈ 4.5 hrs) the drug release significantly ($p < 0.05$) compared to alginate microparticles (ALG). Invitro study proves that drug release was increased at higher pH. The drug release in batch F_1, F_2 and F_3 showed faster release than F_4, F_5 and F_6. But optimum controlled release was observed in the batch $C_1 – C_8$, $H_1 – H_8$ and $E_1 – E_4$ containing Sodium Alginate blended with Carbopol, HPMC and coated with Chitosan. The mechanism of drug release from microspheres was found to be following Case – II transport. From the study it was concluded that controlled release of Nateglinide microspheres can be developed successfully by using Ionotropic Gelation Technique.

Keywords: Microencapsulation, Ionotropic Gelation, Microspheres, Sodium Alginate, Carbopol, HPMC, Chitosan.

INTRODUCTION

Nateglinide is an oral anti-hyperglycaemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the meglitinide class of short-acting insulin secretagogues, which act by binding to β cells of the pancreas to stimulate insulin release. It is administered 120mg per day in two divided doses. The molecule is practically insoluble in water, but almost totally absorbed from gastro-intestinal tract, its biological half-life is 1.5hr and administered twice daily with single dose of 120mg[1]. To overcome the side effects associated with conventional administration of drugs and to increase the patient compliance, controlled release dosage forms have been formulated in the form of Single Unit and Multiunit dosage forms. Compared to Single Unit dosage forms, Multi unit drug delivery system avoid the variations in gastric emptying and different transit rates through the gastrointestinal tract[2], release drugs in a more predictable manner[3], and spread over a large area preventing exposure of the absorbing site to high drug concentration on chronic dosing[4]. Several synthetic polymers have been used to formulate multiunit dosage forms. Recently, much research efforts have been concentrated to develop drug-loaded microspheres using sodium alginate, a natural polymer obtained from marine brown algae, because of simple, mild and eco-friendly preparative conditions.

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MATERIALS AND METHODS

Nateglinide was received as a gift sample from Cadilla Health Care Pvt Ltd., Ahmedabad. HPMC (E50LV) was procured from Aurobindo Pharmaceuticals Ltd., Hyderabad. Chitosan Powder was procured from Central Institute of Fisheries, Cochin, and Kerala. All other chemicals and solvents were of analytical grade satisfying pharmacopoeial specifications.

FORMULATION OF MICROSPHERES[5-19]

Various microspheres were prepared by Ionotropic gelation technique using the formulations as shown in table - 1. In 30ml of aqueous solutions of Sodium Alginate (2% w/v) required amount of Nateglinide was dispersed uniformly and homogenized for 15min. The dispersion was sonicated for 30min to remove any air bubbles that may have been formed during stirring process.

Bubble free dispersion was dropped through a 16 bore glass syringe in a gently agitated calcium chloride solution (2%w/v). After incubating for predetermined time the gelled microspheres were separated by filtration, washed with 3 × 100ml distilled water, air dried overnight and finally dried at 50°C for 6hrs. Similarly microspheres containing Nateglinide prepared by employing Sodium Alginate in combination with different concentrations of Carbopol and HPMC incubated for predetermined times were prepared, washed with 3 × 100ml distilled water, air dried overnight and finally dried at 50°C for 6hrs (Formulation code F_1 to H_8). Later Chitosan coated Alginate microspheres were prepared by making solutions of 1%w/v and 2%w/v of Chitosan add to distilled water containing 0.5%w/v acetic acid adjusted to pH 5.2 – 5.4. The solution was stirred for 1hr. Later this solution was filtered through a muslin cloth to remove impurities. A 2%w/v solution of $CaCl_2$ was added to Chitosan solution. An Alginate/drug solution was added to this solution to form the microspheres. These microspheres were incubated for at different curing times. Later they were decanted, washed with 3 × 100ml distilled water, air dried overnight and finally dried at 50°C for 6hrs (Formulation code E_1, E_2, E_3 E_4) respectively.

Particle size analysis[20]

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. nearly about 100 Microparticles sizes were calculated under 45x magnification.

Morphology of Microspheres

The shape and surface morphology of the microspheres were investigated using JOEL, JSM-6360, Scanning Electron Microscope at 15Kv. Prior to examination, samples were mounted onto stubs by using double sided adhesive tape and vacuum coated with gold film using sputter coater (Edwards-150, UK) to render them electrically conductive. The samples include drug loaded Alginate microspheres, Carbopol blended Alginate microspheres, HPMC blended alginate microspheres and Chitosan coated Alginate microspheres before release study. These above mentioned microspheres were not subjected to Scanning Electron Microscope studies after release because they converted to gel type of matrix when dissolution was over.

Particle sizes of different microspheres were analyzed by optical microscope. Earlier the instrument was calibrated and found that 1 unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 microspheres size were calculated under 45x magnifications for each different formulation.

Swelling Ratio Studies

Swelling ratio of different dried microspheres were determined gravimetrically in slightly agitated phosphate buffer solution of pH 7.4.The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on digital balance (Shimadzu AX-200 corporation, Japan). Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W_0)}{(W_0)} \times 100$$

Where W_0 & W_t are initial weight and Final weight of microspheres respectively.

Determination of Drug Loading Efficiency:

Ten milligrams of drug loaded microspheres from each batch were dissolved in 100ml of Phosphate Buffer solution of pH 7.4 by shaking on a mechanical shaker for 24hrs. The solution was filtered through Whatmann filter paper. An aliquot following suitable dilution was assayed spectrophotometrically (UV-1700 Schimadzu Corporation, Japan) for Nateglinide at 210nm. Drug loading efficiency was determined by using the following relationship:

$$\text{Drug Loading Efficiency:} \quad \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Infrared Spectroscopy

The drug-polymer interactions were studied by infrared spectroscopy. The I.R Spectra were recorded between 500 to 4000 cm^{-1} for Nateglinide, blank Alginate Microspheres, and Drug loaded Alginate Microspheres, Carbopol blended Alginate Microspheres, HPMC blended Alginate Microspheres and Chitosan coated Alginate Microspheres with KBr Pellets using Fourier Transform infrared (FTIR) spectrophotometer (Shimadzu – 8400, Japan).

Differential Scanning Calorimetry

DSC thermograms were performed by using an automatic thermal analyzer system (NETZSCH, DSC 200 PC). The DSC studies on the samples were performed by heating samples at a heating rate of 10°C/min over a temperature range of 50°C – 200°C in a closed aluminum pans.

Statistical Analysis

Each formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variables on DLE and release parameter ($t_{50\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft1 Excel 2002. Difference was considered significant when $p<0.05$.

In-vitro Release Study

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5°C, 75 rpm) using the USP type – II rotating Paddle method in Phosphate Buffer media (pH 7.4, 900ml). A quantity of accurately weighed microspheres equivalent to 100mg Nateglinide each formulation was employed in all dissolution studies. Aliquots of sample were

withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 210nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed phosphate buffer maintaining sink conditions throughout the experiment.

RESULTS

Particle Size Analysis[20]

Table - 1 shows the size of various Microspheres. Microparticles size tends to increase with increase in the initial drug loading. The increase in the size with increase in the drug loading may be attributed to the presence of insoluble drug in the matrix (Formulations F_1 - F_3, C_1 - C_4, H_1 - H_4). However, microparticles size with curing time may be attributed to the progressive gelation of alginate with time.

The increase in the sizes of Cb-ALG, HPMC-ALG with increase in the concentration of carbopol and HPMC (15 – 50%) may be attributed to the increase in the concentration of non-gelling carbopol in the matrix.

The size of Cs-ALG microparticles treated with 1% chitosan (Cs) formulation (E_1) were less, compared to those microparticles coated with 2% chitosan formulation (E_2) for 6hr. Similarly Cs-ALG microparticles coated with 1% Chitosan (formulation E_3) for 24hrs were smaller than those coated with 2% Chitosan (formulation E_4) for 24hrs. The increase in the size with increase in the concentration of external chitosan solution may be attributed to thicker coat induced by high viscous solution. The decrease in the particle size with increase in the curing time (6hr – 24hr) may be due to the higher gelation of alginate in Cb-ALG and HPMC-ALG Microparticles.

Surface Characterization

Fig - 1 shows the surface morphology of drug loaded alginate (ALG), Carbopol-blended alginate (Cb-ALG), HPMC-blended (HPMC-ALG) & chitosan coated alginate (Cs-ALG). Surface of the alginate microparticles appears to be spherical & rough. Similarly the surface of the carbopol blended alginate microparticles (Cb-ALG), HPMC blended alginate microparticles (HPMC-ALG) & Chitosan coated alginate microparticles appears to be rough having few depression compared to drug loaded alginate microparticles (ALG).

Drug Loading Efficiency (DLE):

Drug loading efficiency of microparticles is shown in table - 2. DLE of various formulations was varied depending on the formulation factors such as curing time and initial drug loading. DLE of ALG microparticles (F_1 – F_6) varied from 86.16 to 96.97%. Similarly the DLE of Carbopol-blended, HPMC-blended & Chitosan coated alginate (Cs-ALG) were found to be ≥ 89.14%, 89.81% & 91.14%. The DLE of microparticles prepared by curing 6hr was more compared to those prepared at curing time of 24hrs. Decrease in DLE with increase in curing time may be attributed to higher contact time in calcium chloride solution. Similar decrease in drug loading efficiency (DLE) with increase in curing time was reported by Sankalia etal [7], Halder etal [8]. The DLE of microparticles did not vary ($p>0.05$) with increase in the initial drug loading.

FTIR:

IR spectra of Nateglinide having prominent peaks at the wave numbers of 1213-1386 cm-1 justifying the presence of carboxyl, carboxylate groups, and carbonyl at 1646 cm-1, C-H stretching between at 2857-3030 cm-1, C=O vibration at 1,723 and NH stretching appeared at 3296 cm-1, Alginate microparticles (B) and Drug Loaded Alginate Microparticles (ALG) (C). Comparison of IR spectrum of Drug-loaded Alginate Microparticles (ALG) shows presence of all the peaks of drug. It indicates that drug and excipient (polymer) interaction was not seen in the formulation. It indicates that drug and excipient (polymer) interaction was not seen in the formulation. Similarly other polymers also indicate that the drug was stable in Carbopol blended, HPMC blended and Chitosan coated alginate microparticles.

DSC:

The DSC thermograms of drug (A), Alginate microparticles (B), Drug loaded alginate microparticles (ALG) (C), Chitosan-Coated Alginate Microparticles (Cs-ALG) (D), Drug loaded alginate microparticles (ALG) (C), HPMC-alginate microparticles (HPMC-ALG) (E), Carbopol-alginate microparticles (Cb-ALG) (F) were shown in Figs – 17 & 18 respectively. Figs – 17 & 18 shows a sharp endothermic peak at 157.03^0c which was slightly decreased to 153.24^0c in drug loaded carbopol, HPMC & chitosan coated alginate microparticles. It may be due to the presence of amorphous alginate. Thus it is confirmed that the drug was stable in carbopol-blended (Cb-ALG), HPMC-blended (HPMC-ALG), chitosan coated alginate formulations (Cs-ALG).

Drug release study:

Figs – 2 & 3 shows the dissolution release profiles of alginate microparticles (ALG). The dissolution of drug decreased with increase in the initial drug loading from 5 -15% (Table - 2). $T_{50\%}$ and $T_{80\%}$ values also increased with increase in the initial drug loading. The decrease in the dissolution with increase in the initial drug loading may be attributed to high concentration of insoluble drug in the matrix. As the curing time was increased from 6hr to 24hr, there was a significant ($p<0.05$) increase in the $T_{50\%}$ and $T_{80\%}$ values relative to the results of formulations with different initial drug loading of microparticles cured for 6hr. Increase in the $T_{50\%}$ and $T_{80\%}$ values with increase in the curing time may be due to the penetration of calcium ions to the interior of the microparticles resulting in increased cross linking[7]. Similar results, that decrease in release with increased cross-linking time were reported by Sankalia et al[7]; Halder et al[8]. Similar release profiles of Carbopol-blended (Cb-ALG), HPMC-blended (HPMC-ALG) alginate microparticles in Phosphate buffer pH 7.4 are shown in Figs – 4, 5, 6 & 7. Comparison of $T_{50\%}$ and $T_{80\%}$ values (Table-2) of F_2 formulation with C_1 & H_1 formulations indicate that blending of carbopol and

HPMC controlled the drug release. Furthermore the release of drug was further controlled as the concentration of Carbopol and HPMC was increased in microparticles. The decrease in release of drug from carbopol-blended and HPMC-blended alginate microparticles may be due to the presence of relatively non-ionizing species of Carbopol and HPMC as supported by lower swelling of Carbopol-blended and HPMC-blended alginate microparticles (Figs – 10 & 11). Comparison of $T_{50\%}$ and $T_{80\%}$ values of microparticles cured for 6hr ($C_1 - C_4$) & ($H_1 - H_4$) with those cured for 24hrs ($C_5 - C_8$) & ($H_5 - H_8$) indicate that the release was further retarded due to the increased cross-linking of alginate microparticles. But in case of drug release study of chitosan coated alginate (Cs-ALG) Thu et al[21] reported that positively charged amino groups of chitosan form membranes through ionic interaction with carboxylic residues of alginate and addition of polycationic polymers to the gelation medium results in reduced microcapsule swelling[22,23] and permeability[24]. In the present study, ALG microparticles were dropped in calcium chloride solution containing at different concentrations of chitosan (1 and 2%) and allowed the interaction for two different time intervals (6hr and 24hr). The release profiles of chitosan-alginate (Cs-ALG) are shown in Fig – 8. Coating of alginate microparticles (F2) prolonged the release to 6.5hrs (E2) depending on the concentration of chitosan in the coating solution (1% and 2%). Compared to chitosan-alginate (Cs-ALG) microparticles cross-linked with 1% chitosan solution for 6hr (E1), the Cs-ALG microparticles cross-linked with 1% chitosan solution for 24hr (E2) prolonged the release to 6hr. Treating the ALG microparticles with chitosan solution for 24hrs (E3 & E4) also prolonged the release to 6.5hr significantly ($p<0.001$). Three types of ionic interactions that contribute to the three dimensional cross-linked networks of chitosan/alginate microspheres i.e., the interaction between opposite charges of the biopolymers, the junction formed by the Ca^{+2} and guluronic and mannuronic acid units and inter chain hydrogen bonds[24,25] are responsible for the stability of microspheres, and hence control the release of drug. This was further conformed by slower swelling of Cs-ALG microparticles. (Fig - 12). However, faster release of drug from ALG microparticles was due to the low stability of the chelating junction in a phosphate buffer above pH 5.0 Dainity et al[26].

KINETICS AND MECHANISM OF DRUG RELEASE

In general, the release date from swellable systems can be analyzed according to the following power law expression (Korsmeyer 1983)[28].

$$\frac{Mt}{M\infty} = kt^n \quad \text{----- (1)}$$

Where $Mt/M\infty$ is the fraction of drug released at time, t, 'k' is the proportional constant which accounts for the structural and geometrical properties of the matrix, and 'n' is the diffusional exponent indicative of the mechanism of drug release. The exponent, n, depends on the polymer swelling characteristics and the relaxation rate at the swelling front[5]. The values of release parameters, n and k are inversely related. A higher value of k may suggest burst drug release from the matrix. According to the criteria for release kinetics from swellable systems, a value of release exponent n=0.45, 0.45<n>0.89 and 0.89<n>1.0 indicates fickian (case-I) diffusion, non-fickian (anomalous) diffusion and zero order (case-II) transport, respectively[29]. The initial dissolution profiles (≤ 60%) of the formulations were fitted into equation (1). Using least square procedure the values of 'n' and 'k' for all the systems were calculated and the results along with the values of correlation coefficients (r^2) are presented in table - 2. The 'n' values for ALG microparticles (F1-F6) were between 0.8-1.2. This indicates that the drug release from ALG microparticles followed case-II transport mechanism due to the rapid swelling and erosion of the microparticles. The drug release data of carbopol blended alginate microparticles (Cb-ALG) (C1-C8) also fitted well in the power law of expression and the values of 'n' were between 0.6-0.9 indicating that drug release followed the anomalous transport (or) non-fickian kinetics. The presence of non-ionizing carbopol in Cb-ALG might have controlled erosion. Similarly, the calculated values of 'n' for HPMC blended alginate microparticles (HPMC-ALG) were found to be between 0.6-0.8 indicating anomalous transport due to the presence of HPMC in the matrix which controlled the erosion of microparticles. In case of chitosan formulation (E1-E4) the calculated values of 'n' were between 0.6-0.7 indicating that the swelling was much controlled and the drug release followed the anomalous transport (or) non-fickian kinetics. The drug release studies were also conducted in pH 7.4 and the calculated values 'n', k and r^2 are presented in the table - 2. In case of ALG microparticles the calculated 'n' values were around 1.0 indicating that the release followed case-II transport due to the rapid swelling and erosion of the microparticles. The calculated 'n' values for carbopol blended alginate (Cb-ALG) microparticles were 0.8-1.3, HPMC blended alginate microparticles (HPMC-ALG) were 0.7-0.8 and chitosan coated alginate microparticles (Cs-ALG) was 0.6-0.8 indicating that the drug release followed anomalous transport (or) non-fickian diffusion.

DISSCUSION

In the first part of the work, Nateglinide loaded alginate microparticles (ALG) were prepared by varying the curing time (6hr and 24hr) and drug loading (05, 10 & 15%). The microparticles were spherical with roughness on the surface as shown by scanning electron microscopy studies. The particle size increased with increase in the initial drug loading and decreased slightly with increase in the curing time. Drug loading efficiency was ≥ 87% and was dependent on the formulation variables. The release of ALG formulation was studied in phosphate buffer pH 7.4. The release decreased with increasing the initial drug loading as well as curing time. The release of the drug was always found to be more in phosphate buffer pH 7.4. FTIR and DSC studies did not show any remarkable changes in the drug properties indicating that the drug was stable. Neither increase in curing time nor

initial drug loading prolonged the drug release and drug release completed within 2.5hr. It was thought that rapid ionization of calcium alginate has not been controlled and hence other polymers were blended with alginate. Carbopol-blended alginate microparticles (Cb-ALG) were prepared by replacing a portion of alginate with carbopol. Scanning electron microscopy analysis showed that carbopol-blended alginate (Cb-ALG) microparticles were spherical having smooth surface. The particle size increased with increase in the concentration of carbopol. Drug loading efficiency (DLE) was ≥ 89% and was found to increase with increase in concentration of carbopol. The release of drug from Cb-ALG microparticles decreased with increase in the concentration of carbopol and curing time. The release studies indicated that, the drug release was prolonged to 4.5hr FTIR and DSC studies showed that Nateglinide was stable in carbopol-blended alginate (Cb-ALG) microparticles.

With an intention to study the effect of HPMC on the drug release, a portion of alginate was replaced by HPMC. Scanning electron microscopy analysis showed that HPMC-blended alginate microparticles (HPMC-ALG) were spherical having rough surface. The particle size increased with increase in the concentration of HPMC in the microparticles. Drug loading efficiency (DLE) of HPMC microparticles was ≥ 90% and found to increase with increase in the concentration of HPMC and decreased with increase in the curing time. The release studies indicated that, the drug release was prolonged to 5hr. FTIR and DSC studies of HPMC-blended alginate microparticles (HPMC- ALG) showed that Nateglinide was stable in the formulation.

In the last part of the work chitosan coated ALG microparticles (Cs-ALG) and were prepared. Scanning electron microscopy showed that the microparticles were spherical having rough surface with depressions. The particle size of Cs-ALG microparticles and ALG-Cs-ALG microparticles increased with increase in the coating. The drug loading efficiency (DLE) was ≥ 91%. The release of the drug from Cs-ALG microparticles was 6.5hr in pH 7.4 indicating that the surface pores were plugged and controlled the drug release. FTIR and DSC studies showed that the drug was stable in both Cs-ALG microparticles.

Table 1: Formulation and particle sizes of various microspheres

Formulae	Drug (mg)	Sodium alginate (mg)	Carbopol (mg)	HPMC (mg)	Chitosan (mg)	Glacial acetic acid (%W/V)	Calcium chloride (%W/V)	Curing time (HR)	Particle size (±SD)µM
F_1	66.66	600	---	---	---	---	2	6	803.33±23.09
F_2	105.8	600	---	---	---	---	2	6	828.53±33.49
F_3	200.0	600	---	---	---	---	2	6	888.33±47.60
F_4	66.66	600	---	---	---	---	2	24	646.06±15.49
F_5	105.8	600	---	---	---	---	2	24	785.33±6.80
F_6	200.0	600	---	---	---	---	2	24	702.26±47.07
C_1	105.8	570	30	---	---	---	2	6	1118.86±28.38
C_2	105.8	540	60	---	---	---	2	6	1129.00±27.51
C_3	105.8	510	90	---	---	---	2	6	1220.5±17.66
C_4	105.8	480	120	---	---	---	2	6	1251.06±30.24
C_5	105.8	570	30	---	---	---	2	24	1054.33±8.50
C_6	105.8	540	60	---	---	---	2	24	1126.00±1044
C_7	105.8	510	90	---	---	---	2	24	1176.66±10.06
C_8	105.8	480	120	---	---	---	2	24	1236.33±9.073
H_1	105.8	570	---	30	---	---	2	6	1161.06±18.91
H_2	105.8	540	---	60	---	---	2	6	1149.96±8.78
H_3	105.8	510	---	90	---	---	2	6	1214.43±5.09
H_4	105.8	480	---	120	---	---	2	6	1230.50±33.11
H_5	105.8	570	---	30	---	---	2	24	1110.66±17.47
H_6	105.8	540	---	60	---	---	2	24	1135.33±22.50
H_7	105.8	510	---	90	---	---	2	24	1174.00±13.85
H_8	105.8	480	---	120	---	---	2	24	1214.4±5.13
E1	105.8	600	---	---	600	2	2	6	1256.4±9.58
E2	105.8	600	---	---	1200	2	2	6	1358.4±47.95
E3	105.8	600	---	---	600	2	2	24	1256.20±12.01
E4	105.8	600	---	---	1200	2	2	24	1278.00±13.01

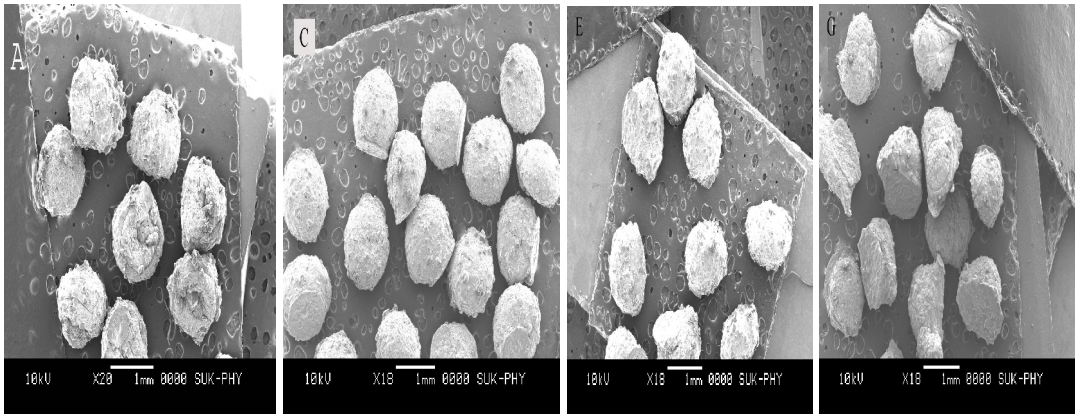

Fig 1: Scanning Electron Micrographs of (A) Drug loaded alginate microparticles (ALG); (C) carbopol-alginate microparticles; (E) chitosan coated alginate microparticles (Cs-ALG); (G) HPMC-alginate microparticles

Table 2: DLE, Dissolution parameters ($T_{50\%}$ & $T_{80\%}$) & Kinetic parameters of dissolution data in Phosphate buffer pH 7.4 described by Korsmeyer-Peppas equation.in phosphate buffer pH 7.4.

Formulation	Drug loading efficiency (DLE) (%w/w) (±SD, n=4)	Phosphate buffer pH 7.4		Phosphate buffer pH 7.4		
		$T_{50\%}$ (min) (± SD) n=4	$T_{80\%}$ (min) (± SD) n=4	n	k	r^2
F1	92.46(0.47)	10.25 (0.50)	62.00 (1.63)	0.9044	0.4840	0.9973
F2	93.72(1.46)	48.00 (0.81)	83.00 (1.15)	1.0664	0.4907	0.9987
F3	94.43(1.87)	78.50 (0.57)	112.75 (0.95)	1.1363	0.1955	0.9925
F4	88.89(1.11)	26.50 (1.00)	70.00 (1.63)	0.9612	0.0118	0.9999
F5	87.72(1.44)	50.25 (2.50)	98.00 (1.63)	1.3554	0.3388	0.9970
F6	86.16(1.39)	83.00 (2.94)	115.00 (2.51)	0.9500	1.5989	0.9987
C1	93.49(3.48)	74.00 (0.08)	116.25 (2.62)	0.8005	0.1579	0.9899
C2	94.74(2.49)	105.25(1.70)	147.25 (1.25)	0.8026	0.7964	0.9962
C3	95.50(2.90)	152.50 (3.78)	193.00 (2.58)	0.8033	0.0861	0.9838
C4	96.90(0.99)	157.75 (4.34)	197.00 (1.15)	0.8334	0.0570	0.9842
C5	89.14(2.24)	77.00 (2.00)	133.00 (2.58)	0.8860	0.4885	0.9900
C6	90.74(1.12)	135.00 (1.15)	190.33 (1.41)	1.3232	0.2962	0.9944
C7	91.87(1.71)	150.00 (1.63)	197.75 (1.70)	0.8001	0.5297	0.9985
C8	92.66(1.56)	156.75 (0.95)	204.00 (1.63)	0.8707	0.2258	0.9948
H1	91.62(1.56)	68.75 (0.95)	150.50 (1.00)	0.8036	0.9958	0.9914
H2	92.35(1.27)	108.00 (1.63)	162.00 (1.63)	0.7591	0.5949	0.9962
H3	93.45(1.74)	148.00 (0.81)	201.25 (0.95)	0.8176	0.3355	0.9905
H4	95.05(1.99)	201.25 (0.95)	240.00 (1.63)	0.8095	0.6538	0.9946
H5	89.81(0.37)	81.50 (1.91)	163.25(1.50)	0.8189	1.0949	0.9904
H6	90.25(0.43)	129.75 (1.70)	189.75 (1.70)	0.8683	0.6889	0.9902
H7	91.75(0.86)	151.50 (1.91)	203.00 (1.15)	0.8028	0.7957	0.9928
H8	92.24(1.54)	236.25 (1.70)	264.00 (1.63)	0.8117	0.6068	0.9950
E1	93.40(1.81)	141.00(1.15)	203.50 (1.91)	0.7433	0.4766	0.9850
E2	94.41(3.75)	165.75 (1.70)	222.00 (1.63)	0.7392	0.5067	0.9905
E3	91.14(1.55)	188.25 (1.70)	256.00 (1.63)	0.7661	0.3150	0.9900
E4	92.97(1.53)	201.75 (1.70)	265.75 (1.25)	0.8234	0.2083	0.9890

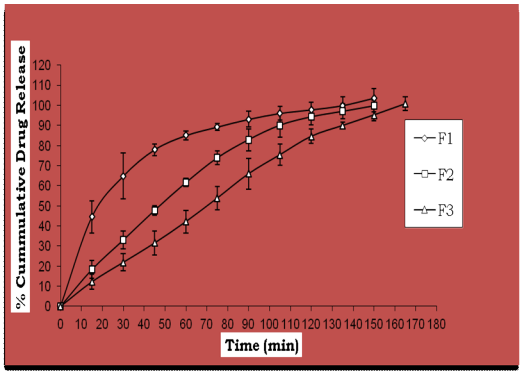

Fig 2: Effect of drug loading on the release profiles of Nateglinide from alginate microparticles (ALG) (curing time 6hr) in phosphate buffer pH 7.4.

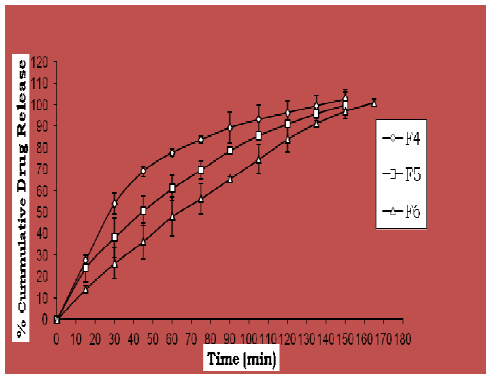

Fig 3: Effect of drug loading on the release profiles of Nateglinide from alginate microparticles (ALG) (curing time 24hr)phosphate buffer pH 7.4.

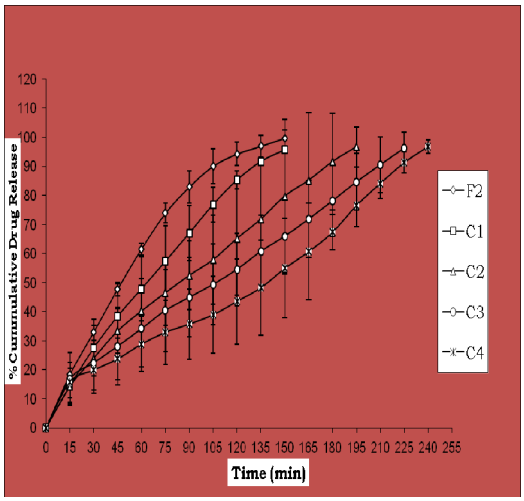

Fig 4: Effect of carbopol concentration on the release profiles of Cb-ALG microparticles (curing time 6hr) in phosphate buffer pH 7.4

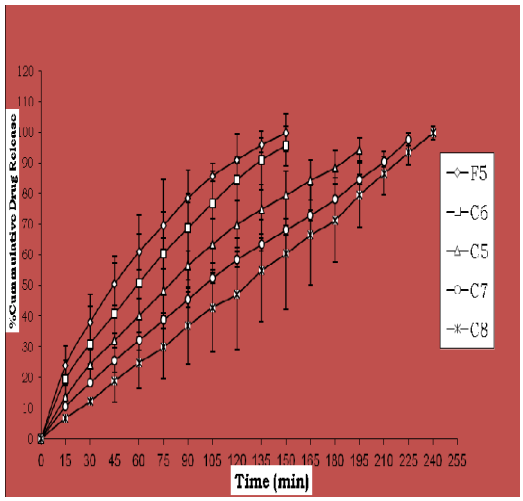

Fig 5: Effect of carbopol concentration on the release profiles of Cb-ALG microparticles (curing time 24hr)in phosphate buffer pH 7.4.

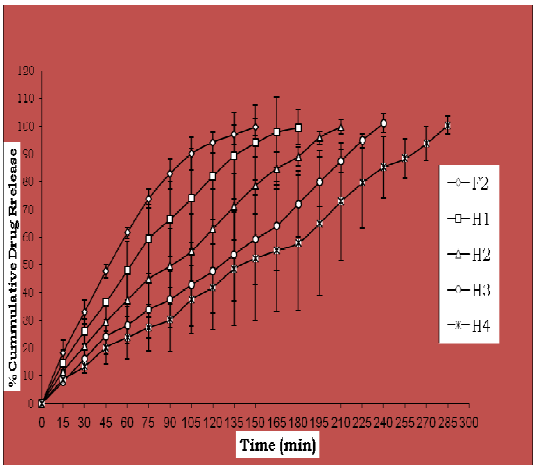

Fig 6: Effect of HPMC concentration on the release profiles of HPMC-ALG microparticles (curing time 6hr) in phosphate pH 7.4.

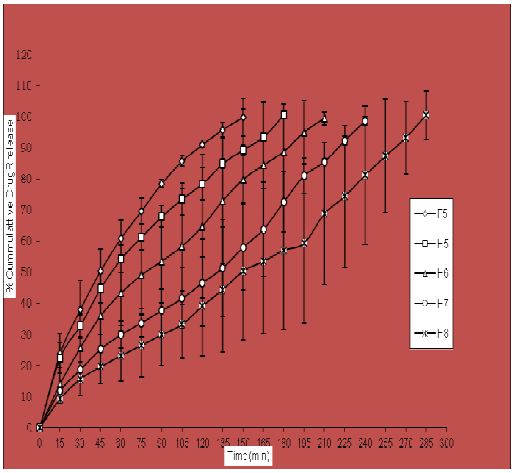

Fig 7: Effect of HPMC concentration on the release profiles of HPMC-ALG microparticles (curing time 24hr) in phosphate buffer buffer pH 7.4.

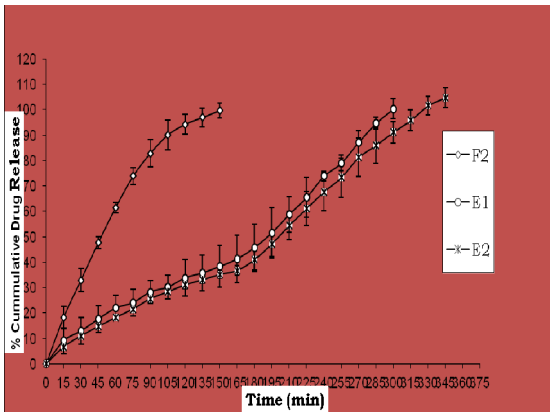

Fig 8: Effect of chitosan concentration on the release profiles of Cs-ALG microparticles (curing time 6hr) in phosphate buffer pH 7.4.

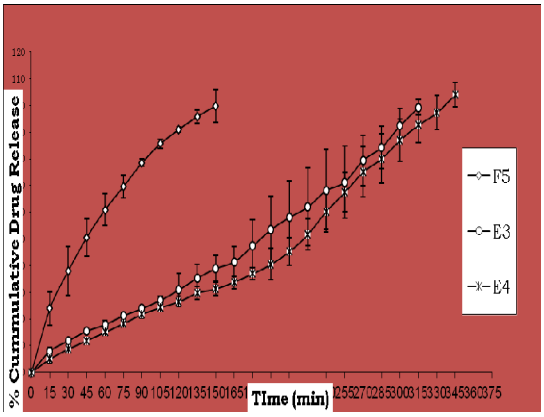

Fig 9: Effect of chitosan concentration on the release profiles of Cs-ALG microparticles (curing time 24hr) in phosphate buffer pH 7.4.

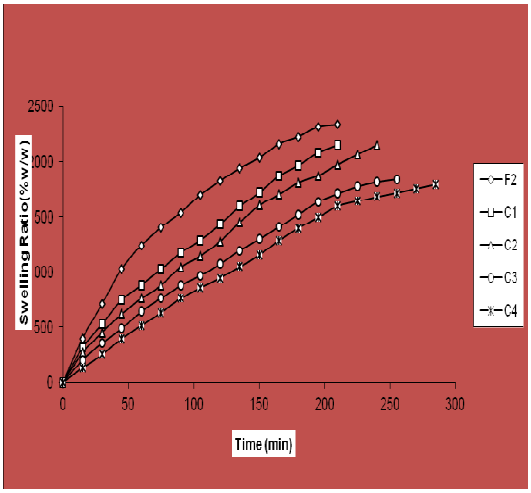

Fig 10: Swelling ratio-time profiles of drug loaded alginate microparticles (ALG); carbopol-alginate microparticles (Cb-ALG).

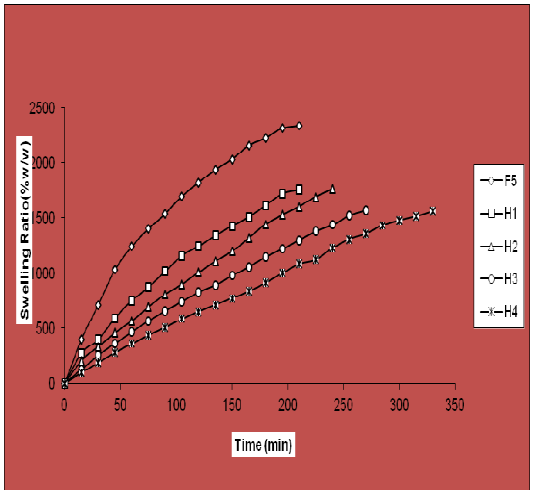

Fig 11: Swelling ratio-time profiles of drug loaded alginate microparticles (ALG) HPMC-alginate microparticles (HPMC-ALG).

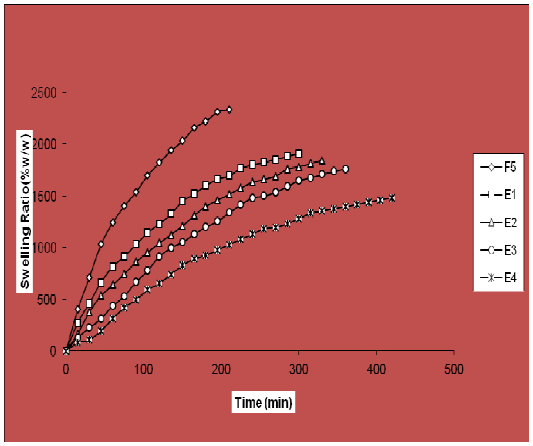

Fig 12: Swelling ratio-time profiles of drug loaded alginate microparticles (ALG); chitosan-alginate microparticles (Cs-ALG).

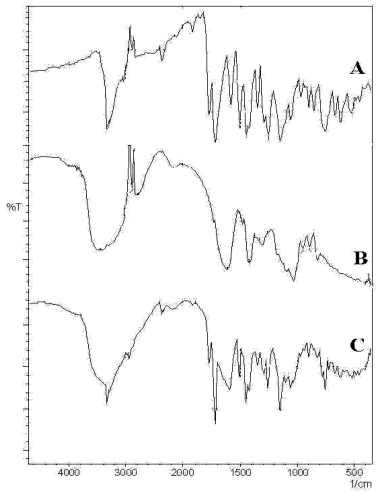

Fig 13: FTIR spectra of (A) drug; (B) alginate microparticles; (C) drug loaded alginate microparticles (ALG).

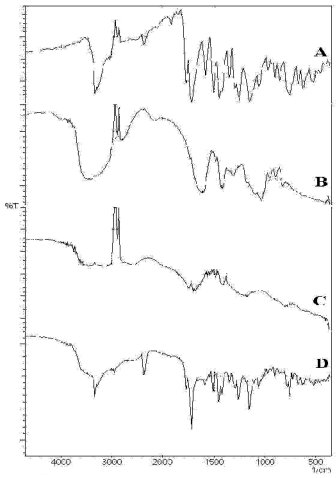

Fig 14: FTIR spectra of (A) drug; (B) alginate microparticles; (C) carbopol (Cb) (D) carbopol-alginate microparticles (Cb-ALG).

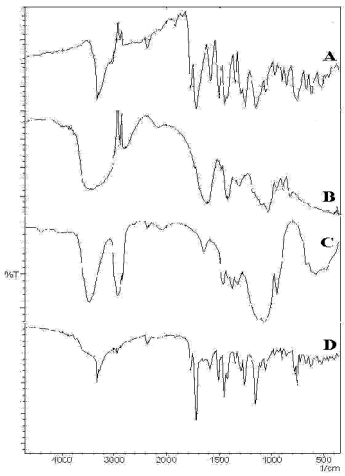

Fig 15: FTIR spectra of (A) drug; (B) alginate microparticles; (C) HPMC (D) HPMC-alginate microparticles (HPMC-ALG)

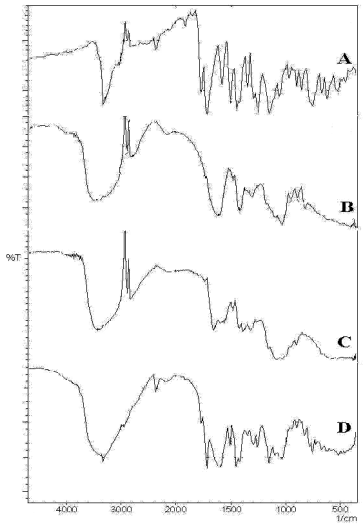

Fig 16: FTIR spectra of (A) drug; (B) alginate microparticles; (C) chitosan (Cs) (D) chitosan-coated alginate microparticles (Cs-ALG).

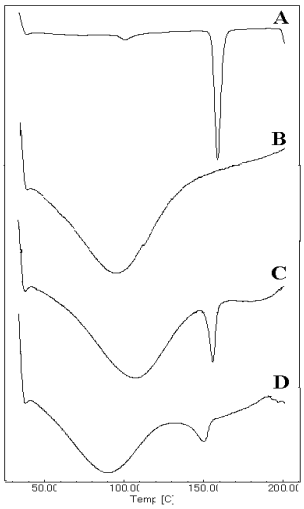

Fig 17: DSC thermogram of (A) drug; (B) alginate microparticles; (C) drug loaded alginate microparticles (ALG); (D) chitosan-coated alginate microparticles (CS-ALG).

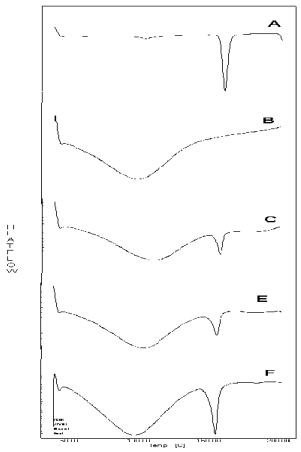

Fig 18: DSC thermogram of (A) drug; (B) alginate Microparticles (C) drug loaded alginate microparticles (ALG); (E) HPMC-alginate microparticles (HPMC-ALG); (F) carbopol-alginate microparticles (Cb-ALG).

CONCLUSION

In conclusion, the ALG microparticles alone cannot prolong the release from weakly acidic drug Nateglinide. The blending of alginate with relatively non-ionizing polymers or formation of polyelectrolyte complex membrane can prolong the drug release in alkaline phosphate buffers of pH 7.4.

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