An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

Research Article

DEVELOPMENT AND EVALUATION OF MICROPARTICULATE SYSTEM FOR CONTROLLED DELIVERY OF ANTIDIABETIC DRUG

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ARTICLE INFO

Key words:

Microencapsulation,
Ionotropic Gelation,
Microspheres,
Sodium Alginate,
Carbopol,
Acrycoat S100,
Guar Gum

ABSTRACT

Nateglinide is an oral anti-hyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Nateglinide loaded alginate microparticles (ALG) were prepared by varying different concentration of Carbopol, Guar Gum, Acrycoat S100 as co-polymersand Cross-linking (or) Gelling agent $CaCl_2$ (2% & 4% w/v) with constant drug concentration of 30% w/w. The particle size decreased with increase in crosslinking agent concentration from 2% to 4% w/v and increased with increase in co-polymer concentration. Drug loading efficiency was ≥ 92.72 % w/v and was dependent on the formulation variables. Drug loading efficiency (DLE) was found to increase with increase in concentration of co-polymers, as well as decreased, with increase in concentration of gelling agent. The drug release decreased with increase in the concentration of gelling agent as well as co-polymer concentration in the alginate matrix. In Conclusion, the ALG microparticles alone cannot prolong the release of 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 (pH 7.4). The present study recommends that Nateglinide controlled Release can be achieved by Ionotropic Gelation Method using Natural Hydrophilic Polymers.

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.

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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.

MATERIALS AND METHODS

Nateglinide was received as a gift sample from Cadilla Health Care Pvt Ltd., Ahmedabad.. Acrycoat S100 Gift sample from corel Pharma Ahmedabad, Carbopol – 934P, Sodium Alginate, Guar Gum, Potassium di hydrogen ortho phosphate, Glacial acetic acid, Methanol, Calcium chloride dehydrate, Potassium di-hydrogen phosphate (KH_2PO_4) obtained from S.D Fine chemicals pvt limited, Mumbai.

FORMULATION OF MICROSPHERES [5 -24]

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% & 4%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,Guar Gum Acrycoat-S100 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 ALG_1 to GG_8). Carboplo-Alginate microsphers containing nateglinide were prepared by replacing few amount of sodium alginate with different concentrations of carbopol 934p. Acrycoat S100-Alginate microsphers containing nateglinide were prepared by replacing few amount of sodium alginate with different concentrations of Acrycoats100.Guar gum-Alginate microspheres containing nateglinide were prepared by replacing few amount of sodium alginate with different concentrations of Guar Gum.

Particle Size Analysis: 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, Acrycoat-S100 blended alginate microspheres and Guargum blended 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.

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.

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

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:

$$\text{DLE} : \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

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, Acrycoat-S100 blended Alginate Microspheres and Guargum 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 analy-

sis 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 [25]: 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 ALG_1– ALG_2, C_1– C_8,AC_1– AC_8, GG1-GG_8). The increase in the sizes of Cb-ALG, AC-ALG and GG-ALG were prepared by varying the % concentration of gelling agent (2% & 4 % w/v $CaCl_2$). The microparticles size tends to decrease with increase of gelling agent The decrease in the size with increase in the concentration of gelling agent may leads to more penetration of extended gel bead calcium ions were due to a more extended gel bead shrinkage during gelation by calcium ions. A similar result of decrease in particle size with increase in the concentration of gelling agent was reported by P.Sriamornsak et al & Giri Prasad et al.

Surface Characterization: Fig - 1 shows the surface morphology of drug loaded alginate (ALG), Carbopol-blended alginate (Cb-ALG), Acrycoats100-blended (AC-ALG) & Guar Gum blended Alginate (GG-ALG). Surface of the alginate microparticles appears to be spherical & rough. Similarly the surface of the carbopol blended alginate microparticles (Cb-ALG), Acrycoat-S100 blended alginate microparticles (AC-ALG) & Guar Gum alginate microparticles(GG-ALG) 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 and initial drug loading. DLE of ALG microparticles (ALG_1 –ALG2) varied from 92.72%. Similarly the DLE of Carbopol-blended, Acrycoat-S100-blended & Guar Gum Alginate (GG-ALG) were found to be ≥ 94.00%, 87.04% & 90.11%. . Decrease in DLE with increase in crosslinking agent may be attributed to higher contact time in calcium chloride solution. Similar decrease in drug loading efficiency with increase in concentration of crosslinking agent was reported by Giri Prasad et al. 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, Acrycoats100 blended and Guar Gum 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 – 19 & 20 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 shows the dissolution release profiles of alginate microparticles (ALG). The dissolution of drug decreased with increase in the cross linking agent from 2 -4%w/v (Table - 2). $T_{40\%}$ and $T_{60\%}$ values also increased with increase in the concentration of crosslinking agent. The decrease in the dissolution with increase in concentration of crosslinking agent may be attributed to high concentration of insoluble drug in the matrix. ($p<0.05$) increase in the $T_{40\%}$ and $T_{60\%}$ values relative to the results of formulations . Increase in the $T_{40\%}$ and $T_{60\%}$ values with increase . Similar results, that decrease in release with increased cross-linking time were reported by Giri Prasad et al; Sankalia et al & Halder et al. Similar release profiles of Carbopol-blended (Cb-ALG), Acrycoats100-blended (AC-ALG) alginate microparticles in Phosphate buffer pH 7.4 are shown in Figs – 4, 5, 6 & 7. Comparison of $T_{40\%}$ and $T_{60\%}$ values (Table-2) of formulation with ALG_1& GG_8 formulations indicate that blending of carbopol,Acrycoats100 and Guargum controlled the drug release. Furthermore the release of drug was further controlled as the concentration of Carbopol,Acrycoat & Guargum was increased in micropar-

ticles. The decrease in release of drug from carbopol-blended and Acrycoats100-blended alginate microparticles may be due to the presence of relatively non-ionizing species of Carbopol, Acrycoats100 and Guargum. Comparison of $T_{40\%}$ and $T_{60\%}$ values of microparticles indicate that the release was further retarded due to the increased cross-linking of alginate microparticles. 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.

KINETICS AND MECHANISM OF DRUGRELEASE:

For understanding the mechanism of drug release and release kinetics of the drug from the dosage form, the In-vitro drug diffusion data obtained was fitted to mathematical model. In general, the release rate from swellable systems can be analyzed according to the following power law expression (Korsmeyer 1983).

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

Where Mt/M_∞ 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. 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. 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 (ALG_1 – ALG_2) were between 0.6 - 1.02. This indicates that the drug release from ALG micropaticles 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) (C_1 - C_8) also fitted well in the power law of expression and the values of 'n' were between 0.6 - 0.8 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 Acrycoat S100 blended alginate microparticles (AC-ALG) were found to be between 0.7 - 0.8 indicating anomalous transport due to the presence of Acrycoat in the matrix which controlled the erosion of microparticles. In case of Guar Gum formulation (GG_1 – GG_8) the calculated values of 'n' were between 0.6 - 0.8 indicating that the swelling was much controlled and the drug release followed the anomalous transport (or) non-fickian kinetics.

DISSCUSION

Nateglinide is an oral anti-hyperglycemic 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 120 mg per day in two divided doses. It has half-life of 1.5 hr. In the first part of the work, Nateglinide loaded alginate microparticles were prepared by varying different concentration of gelling agent $CaCl_2$ (2% & 4% w/v) and constant drug concentration at 30% w/w. The particle size decreased with increase in gelling agent concentration from 2% to 4% w/v and increased with increase in Carbopol 934P, Acrycaot-S100, Guar Gum (co-polymers) concentration. The release from ALG microparticles was studied in Phosphate Buffer pH 7.4. The release decreased with increase in the concentration of gelling agent in the alginate matrix. Increase in gelling agent concentration from 2% to 4% w/v did not prolong the drug release in case of alginate microspheres and drug release completed within 3.5 hrs and 4.0 hrs. It was thought that rapid ionization of calcium alginate could not control the release of the drug and hence other polymers were blended with alginate. Carbopol-blended alginate microparticles were prepared by replacing a portion of alginate with Carbopol 934P. The release of drug from Cb-ALG microparticles, Guar Gum-ALG microparticles, Acrycoat S-100- ALG microparticles decreased with increase in the concentration of carbopol, Guar Gum and Acrycoat S-100 and gelling agent (2% w/v & 4% w/v). The release studies indicated that, the drug release was prolonged to 4.5 and 5.0 hrs incase of Cb-ALG, 5.5hrs and 6.0 hrs incase of Acrycaot S-100, 6.5 hrs and 7.0 hrs incase of GG-ALG microparticles by blending Nateglinide loaded alginate microparticles at various concentrations of different non-ionizing polymers and gelling agent in pH 7.4 respectively. In Conclusion, the ALG microparticles alone cannot prolong the release of 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 (pH 7.4). The present study recommends that Nateglinide controlled Release can be achieved by Ionotropic Gelation Method using Natural Hydrophilic Polymers. Hence, further studies such as *In-vivo* and Clinical Trials are required to conclude the same.

Table 1: Formulation and particle sizes of various microspheres

FORMULAE	Drug (mg)	Sodium Alginate (mg)	Carbopol (mg)	Acrycoat - S 100 (mg)	Guar Gum (mg)	Calcium Chloride (%w/v)	Particle Size (± SD) µm
ALG1	105.4	600	-	-	-	600	595.03±12.19
ALG2	105.4	600	-	-	-	1200	534.83±16.79
C1	105.4	570	30	-	-	600	647.88± 07.10
C2	105.4	540	60	-	-	600	676.06± 05.69
C3	105.4	510	90	-	-	600	702.33± 04.80
C4	105.4	480	120	-	-	600	730.36± 04.17
C5	105.4	570	30		-	1200	608.86± 02.68
C6	105.4	540	60	-	-	1200	629.00± 02.21
C7	105.4	510	90	-	-	1200	650.50 ± 01.66
C8	105.4	480	120	-	-	1200	699.06±0.24
AC_1	105.4	570	-	30	-	600	710.33± 02.50
AC_2	105.4	540	-	60		600	757.00± 00.44
AC_3	105.4	510	-	90	-	600	800.66± 00.06
AC_4	105.4	480	-	120	-	600	840.33 ± 00.07
AC_5	105.4	570	-	30	-	1200	666.06± 01.91
AC_6	105.4	540	-	60	-	1200	710.96±2.78
AC_7	105.4	510	-	90	-	1200	765.43± 01.09
AC8	105.4	480	-	120	-	1200	802.50± 03.11
GG_1	105.4	570			30	600	910.66± 01.47
GG_2	105.4	540			60	600	1035.33±2.50
GG_3	105.4	510			90	600	1174.00±1.85
GG_4	105.4	480			120	600	1204.4±1.13
GG_5	105.4	570			30	1200	845.20±1.01
GG_6	105.4	540			60	1200	956.00±1.01
GG_7	105.4	510			90	1200	1002.06±2.14
GG_8	105.4	480			120	1200	1110.93±2.07

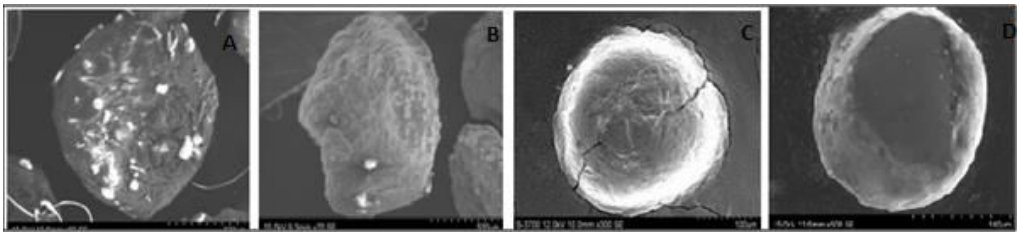

Fig 1: Scanning Electron Micrographs of (A) Drug loaded alginate microparticles (ALG); (B) carbopol-alginatemicroparticles; (C) Acrycoat -S100- Alginate Micro particles (AC-ALG); (D) Guar Gum – Alginate micro particles.

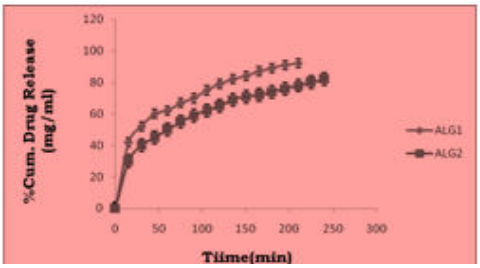

Fig 2: Effect of 2 % & 4 % calcium chloride concentration on the drug release profile of ALG microparticles in phosphate buffer PH 7.4

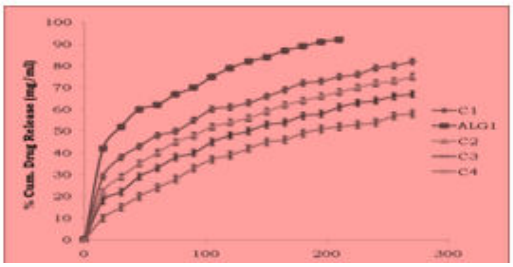

Fig 3: Effect of carbopol and 2 % calcium chloride concentration on the drug release profiles of carbopol-ALG microparticles phosphate buffer PH 7.4

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Table 2: DLE, Dissolution parameters ($T_{40\%}$& $T_{80\%}$) & Kinetic parameters of dissolution data in Phosphate buffer pH 7.4described by Korsmeyer-Peppas equation.in phosphate buffer pH 7.4.

Formulae	Drug Loading Efficiency (DLE) (% w/w) (± SD, n =4)	*In vitro* Release in Phosphate Buffer pH 7.4		Kinetic Parameters in Phosphate Buffer pH 7.4		
		$T_{40\%}$ (min) (± SD) n=4	$T_{60\%}$ (min) (± SD) n=4	N	K	r^2
Alg_1	95.56(0.31)	24 ± 0.02	100 ± 0.11	1.0244	0.3410	0.9973
Alg_2	92.72(0.26)	41 ± 0.32	140 ± 0.54	0.6903	0.2702	0.9987
C_1	96.43(0.62)	36 ± 0.69	120 ± 0.12	0.7343	0.1955	0.9925
C_2	97.23(0.01)	62 ± 0.24	140 ± 014	0.8162	0.1234	0.9999
C_3	98.02(0.02)	90 ± 0.29	170 ± 0.19	0.5994	0.3388	0.9970
C_4	99.06(0.19)	130 ± 0.45	190 ± 0.24	0.6423	0.3291	0.9987
C_5	94.00(0.20)	50 ± 0.12	130 ± 0.18	0.7256	0.1579	0.9899
C_6	95.21(0.03)	90 ± 0.28	155 ± 0.19	0.6654	0.7964	0.9962
C_7	96.00(0.04)	110 ± 0.22	182 ± 0.25	0.6590	0.0861	0.9838
C_8	97.20(0.19)	150 ± 0.97	200 ± 0.14	0.8120	0.0570	0.9842
AC_1	89.04(0.32)	56 ± 0.24	138 ± 0.24	0.8860	0.4885	0.9900
AC_2	93.60(0.22)	100 ± 0.58	161 ± 0.66	0.7862	0.2962	0.9944
AC_3	94.57(0.17)	130 ± 0.65	210 ± 0.58	0.8001	0.5297	0.9985
AC_4	95.17(0.80)	170 ± 0.96	220 ± 0.24	0.8707	0.2258	0.9948
AC_5	87.04(0.56)	70 ± 0.45	145 ± 0.18	0.8036	0.9958	0.9914
AC_6	89.21(0.10)	120 ± 0.58	178 ± 0.25	0.7591	0.5949	0.9962
AC_7	91.23(0.47)	160 ± 0.77	220 ± 0.26	0.8176	0.3355	0.9905
AC_8	93.56(0.11)	210 ± 0.94	270 ± 0.18	0.8095	0.6538	0.9946
GG_1	91.31(0.65)	83 ± 0.48	150 ± 0.97	0.8345	0.0239	0.9904
GG_2	93.70(0.56)	136 ± 0.24	183 ± 0.25	0.8000	0.6889	0.9902
GG_3	95.35(0.34)	177 ± 0.41	242 ± 0.24	0.8218	0.7957	0.9928
GG_4	97.69(0.62)	225 ± 0.11	270 ± 0.42	0.7787	0.6068	0.9950
GG_5	90.11(0.12)	97 ± 0.27	166 ± 0.57	0.6763	0.3150	0.9900
GG_6	92.70(0.35)	150 ± 0.98	197 ± 0.75	0.8009	0.2083	0.9890
GG_7	94.42(0.96)	188 ± 0.24	260 ± 0.55	0.8231	0.3838	0.9900
GG_8	96.77(0.52)	235 ± 0.47	298 ± 0.97	0.7387	0.5792	0.9904

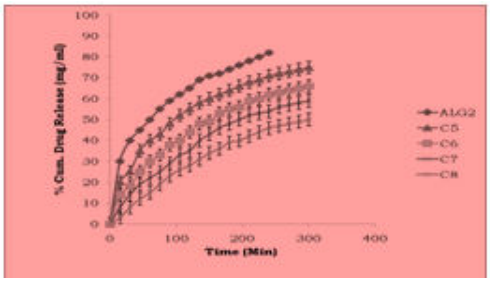


Fig 4: Effect of carbopol and 4 % calcium chloride concentration on the drug release profilesof cb-ALG microparticles in phosphate buffer Ph 7.4

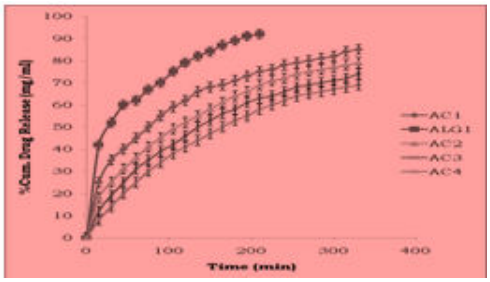


Fig 5: Effect of Acrycoat - S100 and 2 % calcium chloride concentration on the drug release profiles of Acrycoat-S 100-ALG microparticles phosphate buffer Ph 7.4

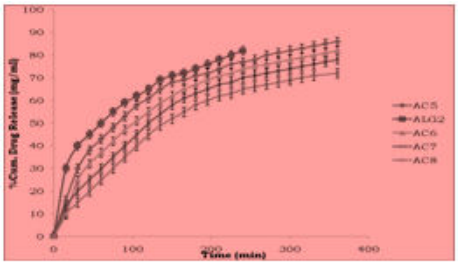


Fig 6: Effect of Acrycoat-S100 and 4 % calcium chloride concentration on the drug release profiles ofacrycoat100-ALG microparticles in phosphate buffer pH 7.4

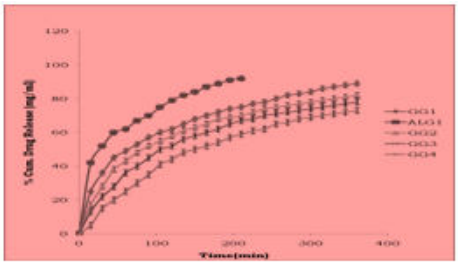


Fig 7: Effect of Guar Gum and 2 % calcium chloride concentration on the drug release profiles of guargum -ALG microparticles in phosphate buffer Ph 7.4

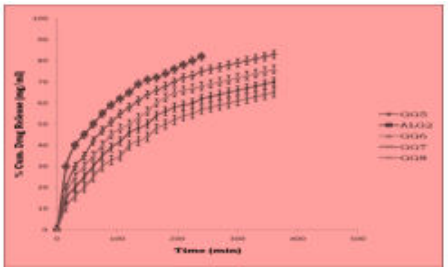


Fig 8: Effect of guar gum and 4 %calcium chloride concentration on the drug release profiles of guargum -ALG microparticles in phosphate buffer pH 7.4.

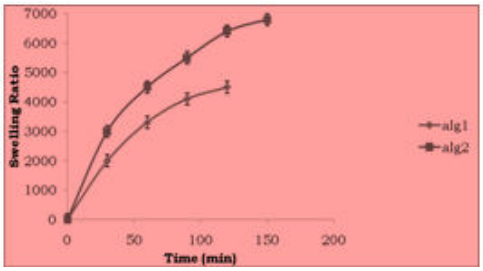


Fig 9: Comparision os swelling ratio-time profiles of drug loaded alginate microparticles (2% & 4% $Cacl_2$)

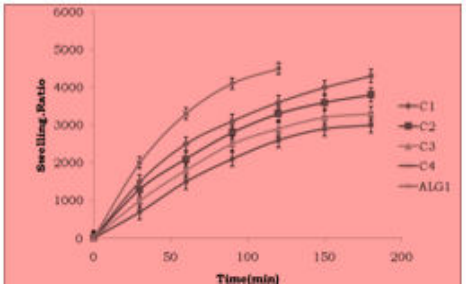


Fig 10: Swelling ratio-time profiles of drug loaded alginate microparticles (ALG); carbopol-alginate microparticles (Cb-ALG).with 2 % calcium chloride

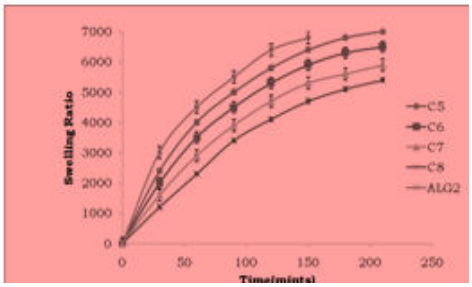
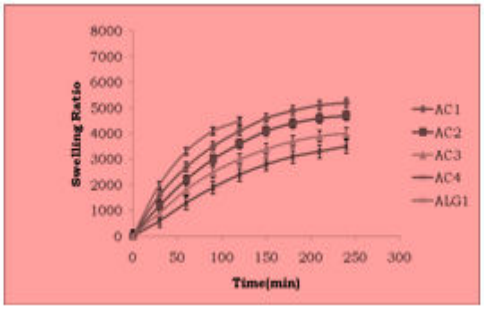


Fig 11: Swelling ratio-time profiles of drug loaded alginate microparticles (ALG) carboplo-alginate microparticles (cb-ALG) with 4 % calcium chloride.



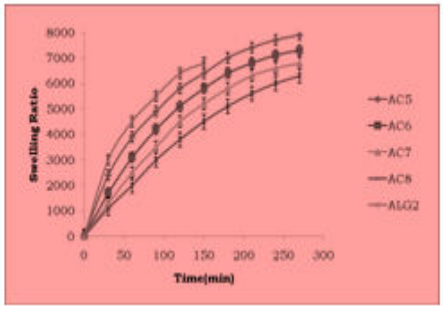


Fig 12: Swelling ratio-time profiles of drug loaded alginate microparticles (ALG); Acrycoats-S100-alginate microparticles (AC-ALG) with 2 % calcium chloride and **Fig 13:** Swelling ratio-time profiles of drug loaded alginate microparticles (ALG) Acrycoats-S100-alginate microparticles(AC-ALG) with 4% calcium chloride

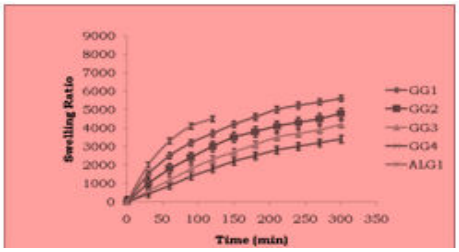


Fig 14:swelling ratio-time profiles of drug loaded alginate (ALG) microparticles, guar gum-alginate microparticles (GG-ALG) with 2 % calcium chloride

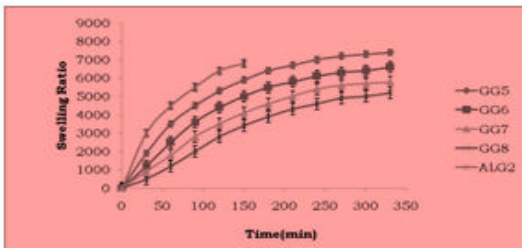


Fig 15: swelling ratio-time profiles of drug loaded alginate (ALG) microparticles guar gum alginate microparticles (GG-ALG) with 4 % calcium chloride.

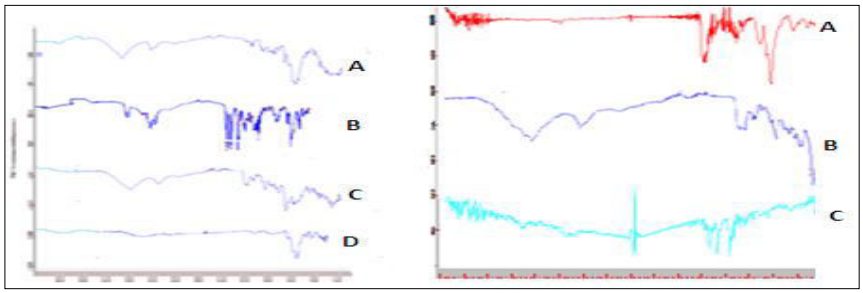


Fig 16: FTIR spectra of (A) Carbopol 934p; (B) nateglinide (C) Sodum alginate (D) (C) Sodium Alginate (D) Guar Gum

Fig 17: FTIR spectra of (A) Acrycoat-S100 (B) Drug loaded alginate microparticles (C) Guar Gum copolymered drug loaded alginate microparticles

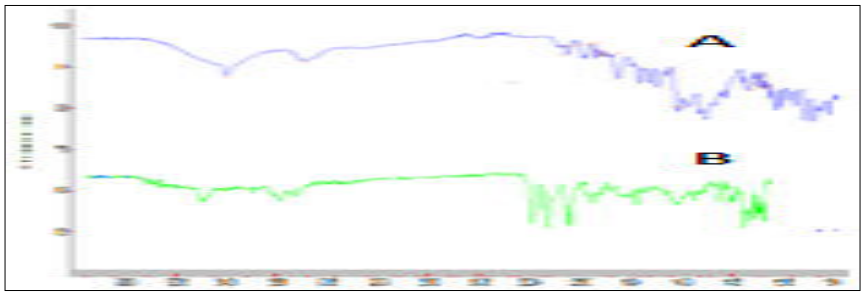


Fig 18: FTIR spectra of carbopol 934p co-polymered Nateglinide loaded alginate (A): (B) alginate Microparticles (B) FTIR spectra of Acrycoat-S100 copolymer drug loaded alginate loaded alginate micro particles (ALG)

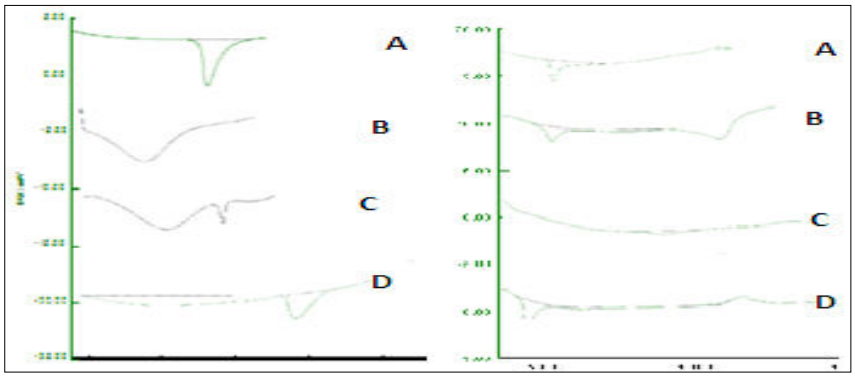


Fig 19: Thermogram of (A) drug; (B) alginate microparticles; (C) Thermogram of drug loaded alginate microparticles (D) Thermogram of carbopol 934p copolymered drug loaded alginate microparticles

Fig 20: DSC thermogram of (A) Acrycoat s100; (B) Thermogram of Acrycoat -S100 co polymered drug loaded alginate Microparticles (C) Thermogram of Guar Gum (D) Thermogram of Guar Gum Co-polymer Drug Loaded Alginate Microparticles.

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.

Acknowledgement

The authors are thankful to Teegala Krishna Reddy College of Pharmacy for providing the facilities to carry out the research work.

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