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Formulation and Evaluation of HPMC/Sodium Alginate/Carbopol Based Pioglitazone Beads

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ABSTRACT

The objective of this study was to develop a tripolymer based beads of pioglitazone and also attempts were made to sustain the release of pioglitazone. Tripolymer beads of pioglitazone were prepared from sodium alginate solution with hydroxy propylmethyl cellulose and carbopol 934 by using curing method**.** These beads were evaluated for bead size, drug encapsulation efficiency, drug loading, FTIR, scanning electron microscopy and in vitro drug release. The release studies were evaluated for the sustain release action of the drug for 12 hours. The experimental and derived quantities have been used to study their dependencies on the nature of the polymeric beads, transport mechanism, encapsulation efficiency and drug diffusion.

Keywords: HPMC, Sodium alginate, beads, pioglitazone

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INTRODUCTION

The hydro gels have the ability to swell and promote the release of encapsulated drugs by controlling cross linking. This makes them attractive as materials in the sustain release (SR) of drugs [1-3]. There are many new polymers useful in the SR applications of drugs and pesticides [4-12]. Sodium alginate (Na-Alg) is a bioerodible polymer that has been widely used in SR applications [13-16] because it forms strong gels in aqueous media and is bioerodible. From a polymer chemistry point of view, the development of interpenetrating network polymers (IPNs) of Na-Alg is attractive because, by definition, the IPNs contain more than one polymer each in a network form, which can be cross linked in the presence of each other to give a three-dimensional network structure producing free volume for the easy encapsulation of drugs. The preparation of IPNs of sodium alginate with carbapol, hydroxyl propyl methyl cellulose. These matrices were used to study the SR of Pioglitazone; an oral hypoglycemic used in the treatment of Type II diabetes mellitus. Pioglitazone has a biological half-life of 3.0-4.0 hrs for a dose containing between 10 and 30mg of the drug. Its short half life can be enhanced by using the tripolymer based beads developed in this research.

EXPERIMENTAL

Materials

Sodium alginate, hydroxyl propyl methyl cellulose, carbapol 934 and calcium chloride were all purchased from s.d. Fine Chemicals, Mumbai, India. Gift sample of Pioglitazone was obtained from Bio-ethical Pharmaceutical ltd., Hubli, India.

Formulation of Pioglitazone beads

Pioglitazone beads were prepared using emulsion-gelation method. Hydroxy propyl methyl cellulose (HPMC), sodium alginate and carbapol 934 are soaked in sufficient amount of distilled water and kept it for overnight. The mixture of HPMC and carbapol is mixed well by using magnetic stirrer. After the formation of a homogenous mixture the drug solution is added slowly and mixed well. With the help of 1ml Insulin syringe the beads were prepared by dropping from a distance of about 10cm. The beads were kept for curing in 1.5%, 2.0% and 2.5% of calcium chloride solution for 15 min ten filtered and dried.

Process variables and process optimization

To investigate the contribution of formulation variables on the release profile of pioglitazone from alginate beads, the different batches were produced and analyzed for size, shape, ease of preparation, drug loading, entrapment efficiency and drug release. The formulation parameters investigated are concentration of sodium alginate, concentration of calcium chloride, concentration of HPMC, concentration of carbapol, percentage entrapment

efficiency and percentage drug loading. These factors were evaluated and experimental trials were performed at all possible levels and 10 formulations were prepared as shown in Table 1.

Table 1: Different formulations prepared

Formulation code	Amount of Pioglitazone (mg)	Amount of sodium alginate	Amount of HPMC	Amount of Carbapol 934	Amount of water (ml)
F1	30	0.3%	0.1%	0.25%	Up to 100
F2	30	0.4%	0.2%	0.25%	Up to 100
F3	30	0.5%	0.4%	0.25%	Up to 100
F4	30	0.8%	0.6%	0.25%	Up to 100
F5	30	1.0%	0.8%	0.25%	Up to 100
F6	30	1.0%	0.9%	0.5%	Up to 100
F7	30	1.25%	1.0%	0.5%	Up to 100
F8	30	1.5%	1.2%	0.5%	Up to 100
F9	30	1.6%	1.4%	0.5%	Up to 100
F10	30	1.7%	1.5%	0.5%	Up to 100

Drying rate study of the beads

A weighed amount of the beads was placed in open glass bottles and kept in an incubator maintained at 37^{o}c. initially the beads were removed at short intervals of time (5,10,15, up to 100min) and later, at longer time intervals (200,300, up to 550 min). These measurements were continued until attainment of constant mass indicating the complete equilibration. All the masses were measured within an accuracy of ±0.01 mg using an electronic micro balance.

EVALUATION OF BEADS

Measurement of bead size

The bead size was measured by taking 5 – 10 particles on a glass slide under polarized light. The mean diameter was calculated by measuring the number of divisions of the eye piece micrometer covering the particles. The stage micrometer was previously used to standardize the eye piece micrometer.

Swelling study of the beads

Swelling property of the beads was studied by measurement of percentage water uptake as a function of time. Three different beads exposed to calcium chloride at different time and at different temperatures were selected and incubated wit distilled water in a watch glass. The mass of all the three beads was taken at different time intervals of time and the average value was calculated. During this process, care should be taken in handling the swollen beads so as to avoid any weight loss due to breaking or erosion of the beads. All the

measurements of the swollen beads were taken on a Mettler single pan balance having accuracy up to fifth decimal. Te percentage uptake of water was calculated as

% water uptake = wet weight – dry weight/dry weight x 100.

Determination of content uniformity and encapsulation efficiency

Beads were evaluated for the pioglitazone content and this was done by incubating the known mass of beads with 5ml of water for complete swelling. The swollen beads were crushed in an agate mortar and pestle and the solution thus formed was sonicated for 2 min using 60 MHz of frequency. Water was evaporated to form a thick paste to which about 10ml of methanol was added to extract all of the pioglitazone. The precipitated Na-Alg was removed from methanol by centrifugation for 5 min at 10,000 rpm. Then the absorbance methanol containing the pioglitazone was taken at 238 nm in a UV spectrophotometer using pure ethanol as a blank.

Percentage encapsulation efficiency was calculated using following formula,

Percentage encapsulation efficiency= AQ / TQ × 1OO

Where AQ is the actual drug content of beads and TQ is the theoretical quantity of drug present in beads. [17].

In-vitro dissolution studies

The in-vitro dissolution studies of floating alginate beads was carried out by using 900ml of 0.1N HC1(pH 1.2) maintained at 37± 0.5 0C at 100 rpm using USP XXIV dissolution test apparatus. The samples were removed periodically and assayed on UV spectrophotometer at 238 nm. [18]

Scanning electron microscope (SEM)

The purpose of SEM study is to obtain topographical characteristics of the beads. The sample was deposited on brass hold and sputtered with gold. SEM photographs were taken with JSM 6400 Scanning Microscope at the required magnification at room temperature. The working distance of 10 mm was maintained and the acceleration voltage used was 15 kV, with ETD as a detector.

RESULTS AND DISCUSSION

To optimize the parameters affecting the formation of beads, experiments were carried out under different conditions. The tripolymer based beads of pioglitazone were prepared by emulsion-gelation method and influence of exposure time to calcium chloride on particle size,

as well as the concentration of HPMC on the release rate of pioglitazone from beads were studied.

Drug encapsulation efficiency ranged from 78.64% to 93.42% and drug loading capacity of beads ranged from 28.91 to 43.23%. There was no considerable effect of exposure time of the beads to calcium chloride on encapsulation efficiency and drug loading capacity of the beads. The percentage encapsulation efficiency was high because bead formation was carried out in calcium chloride in which pioglitazone is insoluble and with a lesser possibility of leaching of pioglitazone during encapsulation. Drug encapsulation efficiency and drug loading capacity of the prepared beads of pioglitazone are shown in the Table 2.

Table 2: Comparative study of pharmaceutical parameters of the pioglitazone beads

Formulations	%DEE	%DL
F1	78.64	31.19
F2	79.21	34.68
F3	79.91	33.69
F4	82.08	31.00
F5	84.68	40.21
F6	89.59	31.91
F7	93.42	43.23
F8	87.11	28.91
F9	82.63	34.12
F10	81.98	30.46

%DEE = % drug encapsulation efficiency, %DL = % drug loading

Microscopical characteristics of the beads

Microscopical characteristics of beads are shown in the Table 3. It was observed that the particle size of the formed beads ranged from 0.7mm to 1.5 mm. The obtained results indicated that particle size of the beads increased on increasing the exposure time to calcium chloride.

Table 3: Particle size and moisture content of the Pioglitazone beads

Formulations	Particle size (mm)	% Moisture content
F1	0.749±0.001	0.99±0.44
F2	0.721±0.03	1.74±0.79
F3	0.735±0.02	2.20±0.59
F4	0.755±0.02	1.28±0.47
F5	0.955±0.02	1.67±0.57
F6	0.736±0.04	1.65±0.56
F7	0.851±0.01	1.82±0.58
F8	0.844±0.05	1.76±0.72
F9	0.917±0.01	1.87±0.73
F10	1.573±0.02	2.30±0.60

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Determination of moisture content

Low moisture content in all the pioglitazone beads indicated the effectiveness of the adopted drying conditions. Low moisture level ensures better stability of the pioglitazone in the beads as shown in Table 4.

Table 4: Percent cumulative release of formulations of the Pioglitazone beads

Formulations	Percent cumulative release		
	T1	T6	T12
F1	17.45	37.23	89.34
F2	19.75	43.53	80.31
F3	16.34	38.22	79.69
F4	21.79	40.53	85.72
F5	22.17	42.32	87.65
F6	19.33	41.72	82.59
F7	22.88	47.38	95.22
F8	21.70	40.20	90.74
F9	21.28	41.90	85.52
F10	21.79	46.71	82.77

SEM of the pioglitazone beads

SEM photographs of the pioglitazone beads given in the Figure. 1 indicates smooth surfaces without any pores.

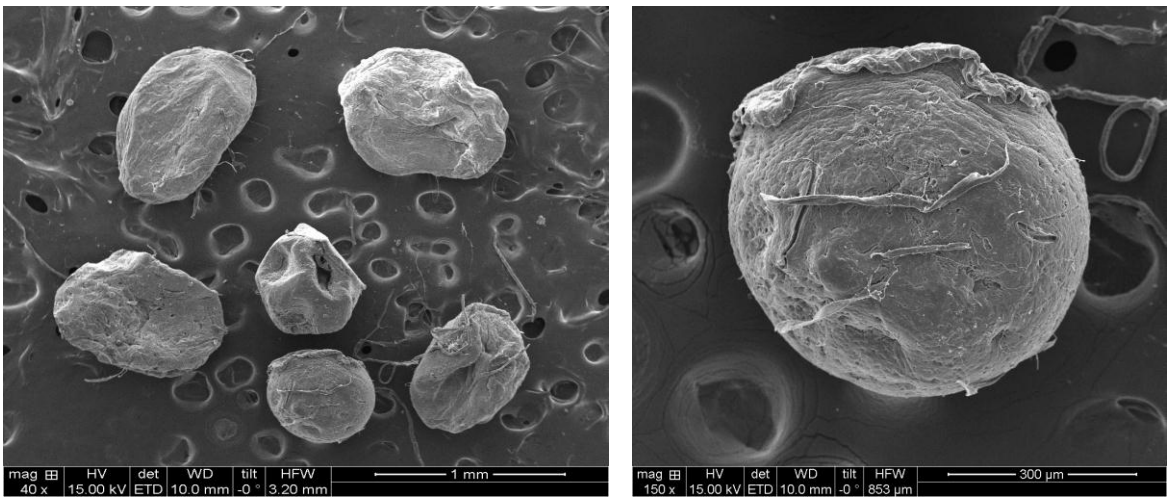

Figure 1: SEM photographs of pioglitazone beads

FTIR spectra

The FTIR spectral values were found almost similar which indicates that the drug is well compatible with the polymers used as shown in table.5 and figure .2.

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Table 5: FTIR spectra

FUNCTIONAL GROUPS	PURE DRUG	DRUG IN POLYMERS
NH-	3416.05	3414.09
C=O	1763.71, 1749.61	1772.62, 1741.78
C – S	711.76	711.78
C – O – C	1147.68	1155.40
C=N	1618.33	1616.09
C=C	1608.69	1614.47
CH – (aliphatic)	2966.62	2976.25
CH – (aromatic)	3084.28	3091.99
C – N	1444.73	1456.30

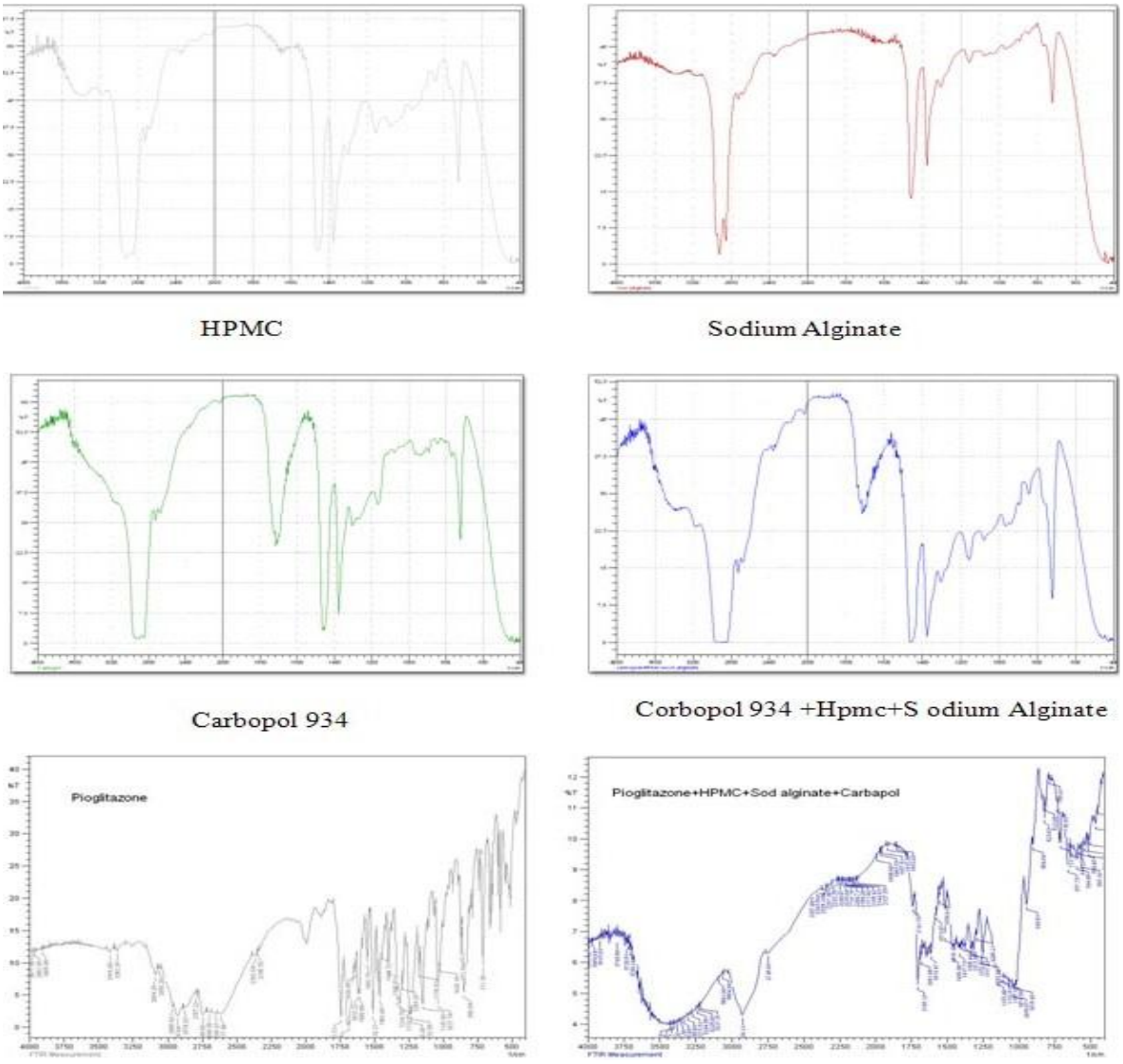

Figure 2: FTIR spectra

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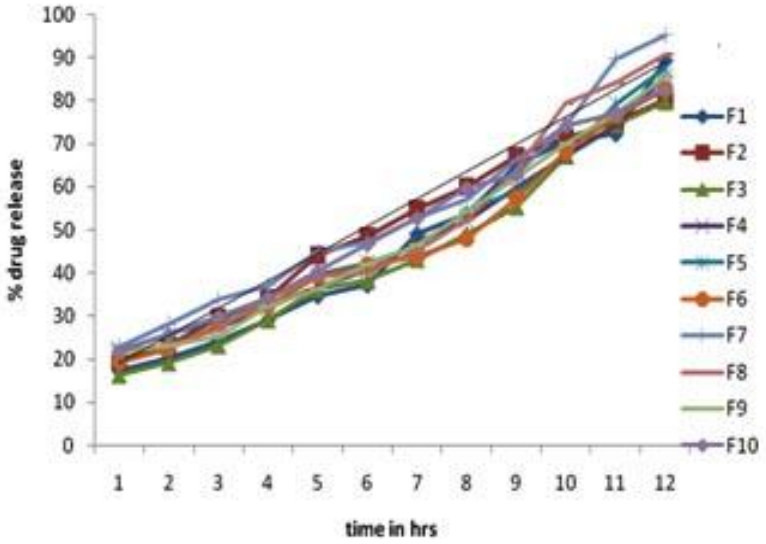

Figure 3: percentage of drug release

In Vitro drug release studies

The in vitro dissolution studies of the formulation F7 shows maximum percent cumulative release with in 12hrs. This shows that F7 was having the good sustained release of the pioglitazone up to the 12 hrs. Hence it can be concluded that a new sustained release system of tri polymer based pioglitazone beads were designed and prepared by an emulsion-gelation method and it's morphological and release characteristics were studied. The prepared beads were easy to prepare and evaluate. The beads showed excellent sustaining properties as compared to the conventional beads which were due to incorporation of three polymers resulting in interpenetrating network.

CONCLUSION

The tripolymer based pioglitazone beads were successfully prepared by emulsion gelation method. Good linearity was shown by the method adopted for the estimation of pioglitazone. The formulated beads have shown higher encapsulation efficiency, drug loading, particle size and very low moisture content. The scanning electron micrographs of beads reveal that the beads are almost spherical. In – vitro dissolution study showed that, amongst the formulations, formulation F7 released pioglitazone for prolonged duration (12hr). This optimized formulation F7 showed best fit in zero order models.

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