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PREPARATION AND EVALUATION OF PREGELATINIZED STARCH MICROSPHERES FOR CONTROLLED RELEASE OF LORNOXICAM

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ABSTRACT

Microspheres are a novel type of controlled/sustained release drug delivery systems to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration. Though several polymeric materials are available for microspheres, there is a continued need for development of new, efficient and cost effective polymers for the preparation of controlled release microspheres. Pregelatinized starch, a partially hydrolyzed starch, is a biodegradable, water dispersible and swell able polymer. The objective of the present study is to develop and evaluate pregelatinized starch microspheres of lornoxicam for control release application. Microspheres with starch or pregelatinized starch alone could not be prepared by conventional microencapsulation methods as they are insoluble in most of the solvents including water. Pre gelatinized starch-alginate microspheres containing lornoxicam could be prepared by ionic-gelation method using an orifice. The microspheres prepared are discrete, spherical, free flowing and are of uniform size (1435µm). Microencapsulation efficiency was in the range 73.6-86.7 %. Lornoxicam release from all the microspheres prepared was slow and spread over 8-12 h and the release was dependent on the composition of the microspheres. Drug release from the microspheres prepared was diffusion controlled and followed first order kinetics. A good linear relationship was observed between percent coat and drug release rate (K_1) of the microspheres the relationship could be expressed by the linear equation, $Y= -0.007X+0.807$ ($R^2=0.987$), where Y is release rate (K_1) and X is percent coat in the microspheres. Pre gelatinized starch-alginate microspheres were found suitable for controlled release application.

KEYWORDS: Microspheres, Lornoxicam, Pregelatinized starch, Orifice method, Controlled release.

INTRODUCTION

Controlled and sustained release drug delivery systems are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. [1] Microspheres have played a vital role in the development of controlled/sustained release drug delivery systems. [2, 3] Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release. Microspheres are matrix systems that contains drug throughout their structure and are potential candidates for oral controlled release. Microsphere can be defined as solid spherical particles ranging from one to 1000 μm in size. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices. Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. A wide variety of polymeric materials, both synthetic and natural have been used for preparation of microspheres. These include natural polymers like albumin, gelatin, collagen, agar, chitosan, dextran; non- biodegradable polymers like polymethyl methacrylate, ethyl cellulose and biodegradable polymers like lactides, glycolides, polyanhydrides etc. Though several polymeric materials are available for microspheres, there is a continued need for development of new, efficient and cost effective polymers for the preparation of controlled release microspheres. Starch is one of the most abundant naturally occurring biodegradable polymers that belong to carbohydrate class. Pregelatinized starch is a partially hydrolyzed starch, which is water dispersible and swellable. No reports are available on the preparation of microspheres employing starch and/ or pregelatinized starch. The objective of the present study is to develop and evaluate pregelatinized starch microspheres for control release application. Lornoxicam, an effective non-steroidal anti-inflammatory drug (NSAIDS) that requires controlled release owing to its short biological half-life, [4] of 3.0 h was used as the core (medicament) in the pregelatinized microspheres to obtain controlled release.

EXPERIMENTAL

Materials

Lornoxicam (gift sample from M/s Hetero Drugs Ltd., Hyderabad), Potato starch, sodium alginate and calcium chloride were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

METHODS

Preparation of Pregelatinized Starch-Alginate Microspheres

Potato starch (1.0 g) and sodium alginate (1.0 g) were taken in water (50 ml) in a beaker and the mixture was heated to boiling while stirring to gelatinize starch and to form viscous mucilage. The drug (100 mesh) was added to the gelatinized starch-alginate mucilage and dispersed. The drug loaded gelatinized starch-alginate mucilage was taken into a syringe and pressed through a needle (no.22) to obtain a succession of spherical droplets. The droplets were collected into a curing solution of calcium chloride (10%w/v) and allowed for curing reaction for 30 min. The hardened microspheres were collected by filtration and dried at 70˚C until dry.

Estimation of lornoxicam

An UV Spectrophotometric method based on the measurement of absorbance at 380nm in phosphate buffer of pH 6.8 was used for the estimation of lornoxicam. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95% and 1.25% respectively. No interference by the excipients used in the study was observed.

Size Analysis

Size analysis of the microspheres prepared was done by sieving using standard sieves.

Estimation of Drug Content in the Microspheres

Microspheres (500 mg) were taken in a dry mortar, finely powdered and mixed thoroughly. Powder equivalent to 20 mg of drug was taken in to a 50 ml conical flask and extracted repeatedly with 3x20 ml of 0.1N NaOH and the extracts were collected in to 100 ml volumetric flask and made up to volume with 0.1N NaOH. The solution was suitably diluted with phosphate buffer of pH of 6.8 and assayed for lornoxicam content at 380 nm.

Microencapsulation Efficiency

Microencapsulation efficiency was calculated using the following formula: Microencapsulation efficiency = (estimated percent drug content/theoretical percent drug content) × 100.

Drug Release Study

Lornoxicam release from the microspheres prepared was studied employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. Phosphate buffer of pH 6.8(900 ml) was used as dissolution fluid. Microspheres (100 mg) were used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for lornoxicam. at 380 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn. Each dissolution experiment was run in triplicate (n=3).

Analysis of Drug Release Data

Drug release data were analyzed as per zero order, first order, Higuchi. [5] and Korsmeyer-Peppas. [6] kinetic equation models to assess the release kinetics and mechanism**.**

RESULTS AND DISCUSSION

The objective of the present study is to develop and evaluate pregelatinized starch microspheres of lornoxicam for controlled release application. Microspheres with starch or pregelatinized starch alone could not be prepared by conventional microencapsulation methods as they are insoluble in most of the solvents including water. Pregelatinized starch-alginate microspheres could be prepared by an ionic-gelation method using an orifice.

The method developed involves the following steps:

1. Starch and sodium alginate were taken into water in a beaker and the mixture was heated to boiling while stirring to gelatinize starch and to form viscous mucilage.
2. The drug powder (100 mesh) was added to the gelatinized starch-alginate mucilage and dispersed.
3. The drug loaded gelatinized starch-alginate mucilage was taken into a syringe and pressed through a needle (no.22) to obtain a succession of spherical droplets.
4. The droplets were collected into a curing solution of calcium alginate (10%w/v) and allowed for 30 min for curing reaction.
5. The hardened microspheres were collected by filtration and dried at 70˚C until dry. Lornoxicam microspheres were prepared using different ratios of coat (pregelatinized starch-alginate): core (lornoxicam). All the microspheres prepared were evaluated for size, drug content, microencapsulation efficiency and drug release characteristics.

All the microspheres prepared were found to be discrete, spherical and free flowing. The method gave uniform sized microspheres (Fig.1). The size of microsphere was 12/16 mesh (1435µm). The drug content and micro encapsulation efficiency of various microspheres prepared are given in Table 1. Low c. v. values (< 2.25 %) in the drug content ensured uniformity of the drug content in each batch of microspheres prepared. The microencapsulation efficiency was in the range 73.6-86.7 % with various microspheres.

Lornoxicam release from the microspheres prepared was studied in phosphate buffer pH 6.8. The drug release profiles of various microspheres prepared are shown in Fig.2. The drug release parameters are given in Table 3. Lornoxicam release from all the microspheres prepared was slow and spread over 8-12 h and the release was dependent on the composition of the microspheres.

Table 1: Drug content and microencapsulation efficiency of lornoxicam microspheres prepared.

S. No	Micro spheres	Drug Content Estimated (mg/100 mg)	CV in percent drug content (%)	Microencapsulation Efficiency (%)
1	LF_1	7.36±0.162	2.20	73.6
2	LF_2	15.94±0.360	2.25	79.7
3	LF_3	32.53±0..137	0.42	81.3
4	LF_4	43.35±0.114	0.26	86.7

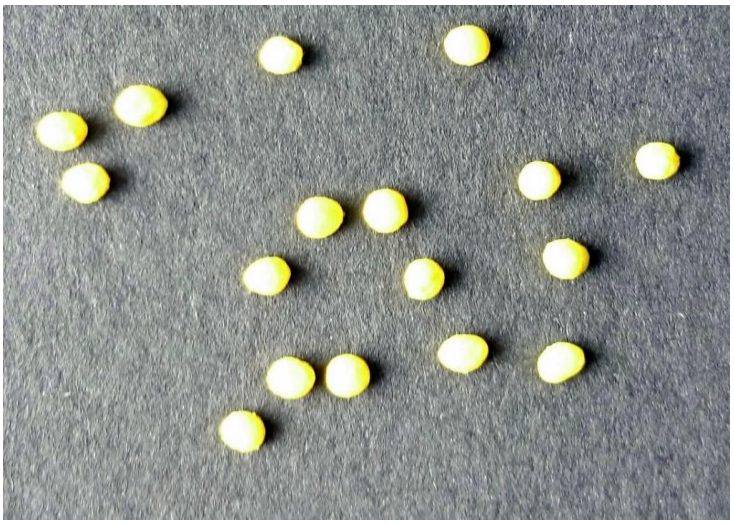

Fig. 1: Photo micrographs of pregelatinized starch - alginate microspheres.

The drug release data were analyzed as per zero order, first order, Higuchi and Korsmeyer-Peppas kinetic equation models to assess the release kinetics and mechanism. The coefficient

of determination values (R^2) observed in the analysis of release data as per various kinetic models are given in Table 2. The R^2 values were higher in the first order model than those in the zero order model indicating that the drug release from all the microspheres prepared followed first order kinetics. The first order drug release profiles of various microspheres prepared are shown in Fig.3. Drug release data also obeyed Higuchi and Korsmeyer-Peppas equation models with $R^2 > 0.949$. All the Higuchi plots were found to be linear indicating diffusion controlled drug release from the microspheres prepared. When the release data were analyzed as per Korsmeyer-Peppas equation, the release exponent 'n' was in the range 0.949-0.991indicating non-fickian diffusion as the release mechanism from the lornoxicam microspheres prepared. A good linear relationship was observed between percent coat and drug release rate (K_1) of the microspheres (Fig.4). The relationship could be expressed by the linear equation, $Y= -0.007X+0.807$ ($R^2=0.987$), where Y is release rate (K_1) and X is percent coat in the microspheres. As such drug release rate from the microspheres can be controlled by varying the percent coat.

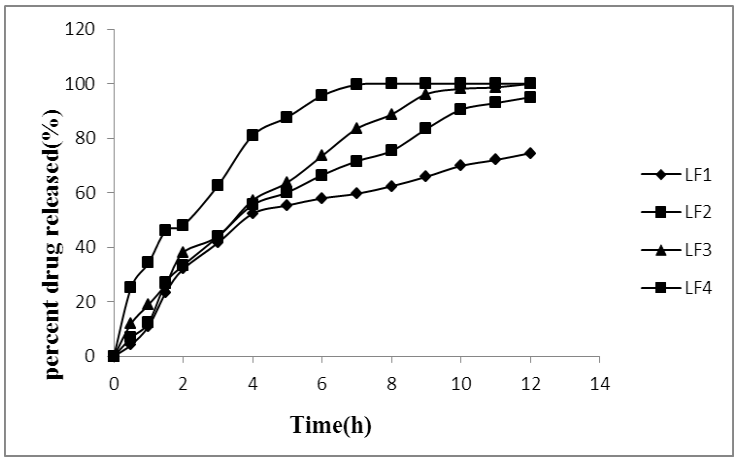

Fig. 2: Drug release profiles of lornoxicam microspheres prepared.

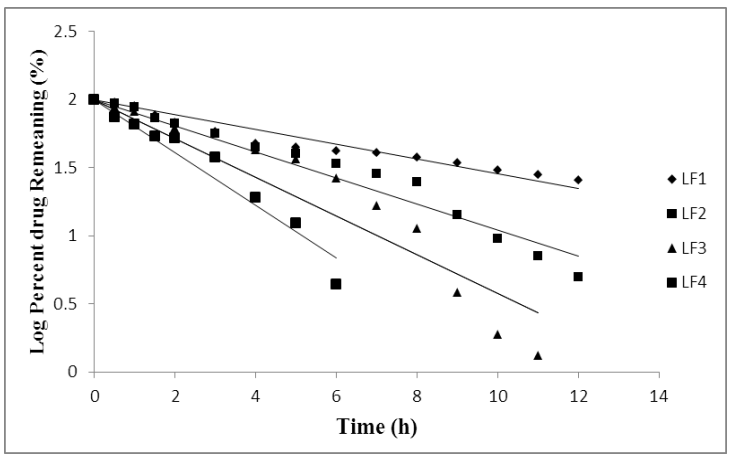

Fig. 3: First order drug release profiles of lornoxicam microspheres prepared.

Table 2: Coefficient of determination (r^2) values in the analysis of drug release data as per various kinetic models.

Formulation	R^2 Value			
	Zero order	First order	Higuchi	Kors meyers peppas
LF_1	0.931	0.978	0.980	0.949
LF_2	0.973	0.983	0.990	0.979
LF_3	0.970	0.967	0.992	0.991
LF_4	0.964	0.973	0.995	0.995

Table 3: Drug release parameters of lornoxicam microspheres prepared.

Formulation	T_{50} (h)	T_{90} (h)	Drug release rate		Release exponent(n)
			K_0 (mg/h)	K_1 (h^{-1})	
LF1	3.75	>12	0.587	0.124	0.75
LF2	3.50	10	1.654	0.210	0.79
LF3	3.25	8.25	3.60	0.332	0.81
LF4	2.25	5.25	5.87	0.444	0.87

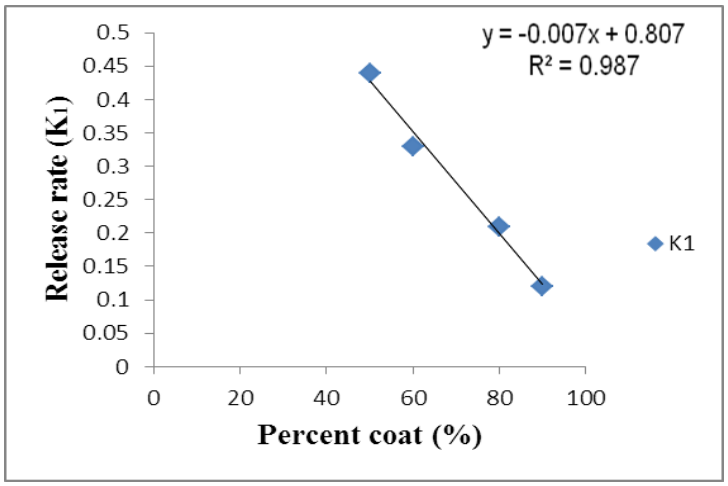

Fig.4: Relationship between percent coat and drug release rate of the microspheres.

CONCLUSIONS

1. Microspheres with starch or pregelatinized starch alone could not be prepared by conventional microencapsulation methods as they are insoluble in most of the solvents including water.
2. Pre gelatinized starch-alginate microspheres containing lornoxicam could be prepared by ionic-gelation method using an orifice.
3. The microspheres prepared are discrete, spherical, free flowing and are of uniform size (1435µm).
4. Microencapsulation efficiency was in the range 73.6-86.7 %.

5. Lornoxicam release from all the microspheres prepared was slow and spread over 8-12 h and the release was dependent on the composition of the microspheres.
6. Drug release from the microspheres prepared was diffusion controlled and followed first order kinetics.
7. A good linear relationship was observed between percent coat and drug release rate (K_1) of the microspheres
8. Pre gelatinized starch-alginate microspheres were found suitable for controlled release application.

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