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Original Article

Gelatin beads as sustained release drug delivery system

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Abstract

In the present context, an attempt to improve the performance of gelatin beads as sustained release drug delivery via the emulsion cross linking method, was undertaken. Hence, two types of polymers, gelatin (type B) and fish gelatin were used for the preparation of gelatin beads by Emulsion cross linking method. Gelatin (type B) as a polymer proved helpful during the process of formulation development. Drug excipient compatibility studied by IR spectroscopy and DSC confirmed no interaction between the drug and the excipient. Gelatin beads of Propranolol HCl were prepared by loading. The formulation was subjected to performance evaluation. Entrapment efficiency and %drug release of batches F1 to F9 were considered for the selection of optimized batch. Batch F9 was selected as it possessed the highest potential to release the drug gradually for more than 11hr with highest entrapment efficiency 92.38 ± 0.97 %. Gelatin beads were filled in hard gelatin capsules and subjected to evaluation. Accelerated stability studies were carried out.

Key words: Gelatin beads, Fish gelatin, propranolol HCl, sustained release drug delivery, emulsion cross linking method

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1. Introduction

Beads can be used for the sustained release of drugs, vaccines, antibiotics, and hormones. For example, by taking advantage of the characteristics of beads, beyond the basic benefits, the beads could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior. The method that is described in this study is achieved with natural polymers. The main advantages of natural polymers are that they are biocompatible, biodegradable and produce no systemic toxicity on administration. Preparation and evaluation of beads of Propranolol HCL with biodegradable natural polymers fish gelatin and gelatin B as carriers by using physical cross-linking to avoid toxicity of chemical cross-linking agents has been attempted to obtain a suitable oral sustained drug delivery

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which can overcome the disadvantages of the selected drug.[1]

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may also be a mixture of both types. The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15000–250 000. Gelatin is practically odourless and tasteless. It is insoluble in acetone, chloroform, ethanol (95%), ether, and methanol. It is soluble in glycerine, acids, and alkalis, although strong acids or alkalis cause its precipitation. It swells and softens in water, gradually absorbing 5 to 10 times its own weight in water. It solubilizes in hot water. Upon cooling to 35–40 °C, it forms a jelly or gel. At temperatures 40 °C, the system exists as a sol. A gel of higher viscosity is formed in alkaline media as compared with acid media (3). Because it is a protein, gelatin exhibits chemical properties characteristic of those materials (e.g., gelatin is hydrolysed by most of the proteolytic systems to yield its amino components). Gelatin reacts with acids and bases, aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, and surfactants.[2]

2. Materials and method:

Propranolol HCl, Gelatin Type -B, Fish Gelatin, Glutaraldehyde, were obtained from Research Lab Fine Chem Industires Mumbai. Tween 80 was obtained from Hi Media Laboratories Pvt. Ltd. Mumbai. And all other chemicals used are of analytical grade.

Method of preparation

Emulsion cross linking method:- In this method, drug was dissolved in aqueous gelatin solution, which was previously heated for 1 hr at 40^0C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35^0C, resulting in w/o emulsion. Further stirring was done for 10 min at 15^0C. The produced beads were washed three times with acetone and isopropyl alcohol, respectively, air- dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking. Afterward, beads were treated with 100mL of 10mm glycine solution containing 0.1%w/v of tween 80 at 37^0C for 10 min to block un-reacted glutaraldehyde.[3]

Evaluation of gelatin beads

A) Loading of Propranolol HCL on Gelatin beads

1mg of Propranolol HCL drug was taken in 100ml distilled water. stirring was done continually to dissolve the drug in distilled water.The drug was loaded allowing the gelatin beads (5gm) at 37 ± 0.2^0C under continuous magnetic stirring (200 rpm) in a water solution of Propranolol HCL(1mg:100 ml) for 15 min. After this time period, the drug-loaded gelain beads were collected by rapid filtration, washed with water and then lyophilised.[4]

B) Evaluation of Propranolol HCL Gelatin beads

i) Entrapment efficiency

1gm of drug loaded gelatin Type-B beads was placed in100 ml

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phosphate buffer, pH 7.4, and mechanically agitated on shaker at 200 rpm for 24 h. The resultant dispersions were filtered and analyzed at 289 nm using UV spectrophotometer. The percentage drug entrapment efficiency (% EE) of each bead formulation was calculated using the following equation[5]:
EE% = Practical drug content/ Theoretical drug content × 100

ii) % Yield

Practical yield is calculated to estimate the efficiency of any method, ,thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of beads recovered from each batch in relation to the sum of starting material. The percentage yield of prepared beads was determined by using the formula,[6]

Percentage yield = Practical yield/Theoretical yield ×100

iii) In vitro Drug release

The dissolution studies were performed by using USP II (Paddle type).The dissolution studies were Performed in pH 6.8 Phosphate buffer at 100rpm at temp 370C ± 0.50C. During dissolution study 1ml aliquot was withdrawn at different time intervals Of 10, 20,30,40,50 and 60 min, same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatmann filter paper No.42 and absorbance values were measured at 289nm.[7]

C) Selection of suitable source for gelatin beads [Gelatin(Type-B) and Fish Gelatin]

According to above evaluation parameters Gelatin (Type-B) was selected as a suitable source for preparation of Gelatin Beads.

Filling and Evaluation of Drug loaded gelatin beads in to hard gelatin capsules

A) Filling of Drug loaded Gelatin beads in to Hard Gelatin capsules

The encapsulation process consists of filling hard gelatin capsules with one or more bead populations using a commercial capsule filling equipment. MG future, equipped with two bead-filling hoppers.MG Futura consist of 32 dosing segments and can produce 96,000 capsules per hour To manufacture capsule dosage forms, the shell hopper on the Futura is filled with empty capsule while one or both bead dosing hoppers are filled with the test beads, and the valve on hopper 1 is opened to deliver the amount of beads required to fill each capsule based on the potency of the beads. According to the yield value calculations it is evident that 500mg of optimized drug loaded gelatin beads corresponds to 100mg Propranolol HCL.[6]

A) Evaluation of Hard Gelatin capsules

1. Dissolution studies

Drug loaded gelatin beads were filled in hard gelatin capsules of dose equivalent to 100mg of propranolol HCL in capsule dosage form were subjected to dissolution test. The dissolution medium was 900ml (pH 6.8 Phosphate buffer USP)

Speed	Temperature	Apparatus
50RPM	$37^0C \pm 0.5^0C$	Basket USP type- II

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During dissolution study 1ml aliquot was withdrawn at different time intervals of 10, 20, 30, 40, 50 and 60 min, same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatmann filter paper no. 42 and absorbance values were measured at 289 nm.[7]

Accelerated stability studies

Formulation F-9 which is reformulated batch of gelatin bead was kept for accelerated stability studies according to ICH guidelines. Formulations were sealed in aluminium packaging coated inside with polyethylene. The studies were performed at $4^0C \pm 2^0C$ and 75%±5 relative humidity (RH) in the stability chamber for up to 3 months. A physical inspection, saturation, drug content and invitro drug release were conducted periodically (initial, 1, 2, 3 months) for the entire period of stability study.[9]

Assay

The exicipient compatibility of drug and the excipient was studied their physical mixture in ratio 1:1. The mixtures were prepared by triturating the drug with excipient and the solutions were stored for 24 hrs at room temperature. Then the mixture was titrated with an aliquot of the drug solution containing 1.0-20.0 mg of Propranolol HCL. Propranolol HCL was measured accurately and transferred in to a clean and dry 100ml titration flask and the total volume was brought to ml with glacial acetic acid. Then 3ml of 3% mercury acetate (Hg(OAc)2) was added, the content was mixed, and after 2 min, two drops of crystal violet indicator were added and titrated with standard 0.01 M perchloric acid to a blue end point. The amount of the drug in the measured aliquot was calculated based on the formula [8]

$$Amount(mg) = VMwR/n$$

Where,

V= volume of perchloric acid required, ml
Mw= relative molecular mass of the drug
g = molarity of the perchloric acid
n= number of moles of perchloric acid reacting with each mole of Propranolol HCl

3. Result and discussion

A. Evaluation of Gelatin(Type-B) and Fish Gelatin

Table No. 2 shows the result of evaluation parameters of gelatin type-B and fish gelatin beads such as bulk density, tapped density, hausners ratio, compressibility index and angle of repose.

B) Selection of suitable source for Gelatin beads [Gelatin (Type-B) and Fish Gelatin]

From the above formulations evaluated for their % entrapment efficiency. It is quite evident from the data depicted in Table No.3 that as the increase in the Gelatin (Type-B) concentration increases %yield and %EE increases. This was due to the fact for that the bloom strength of gelatin (Type-B) is high causing them to interact with more polymer and thereby increasing %EE.

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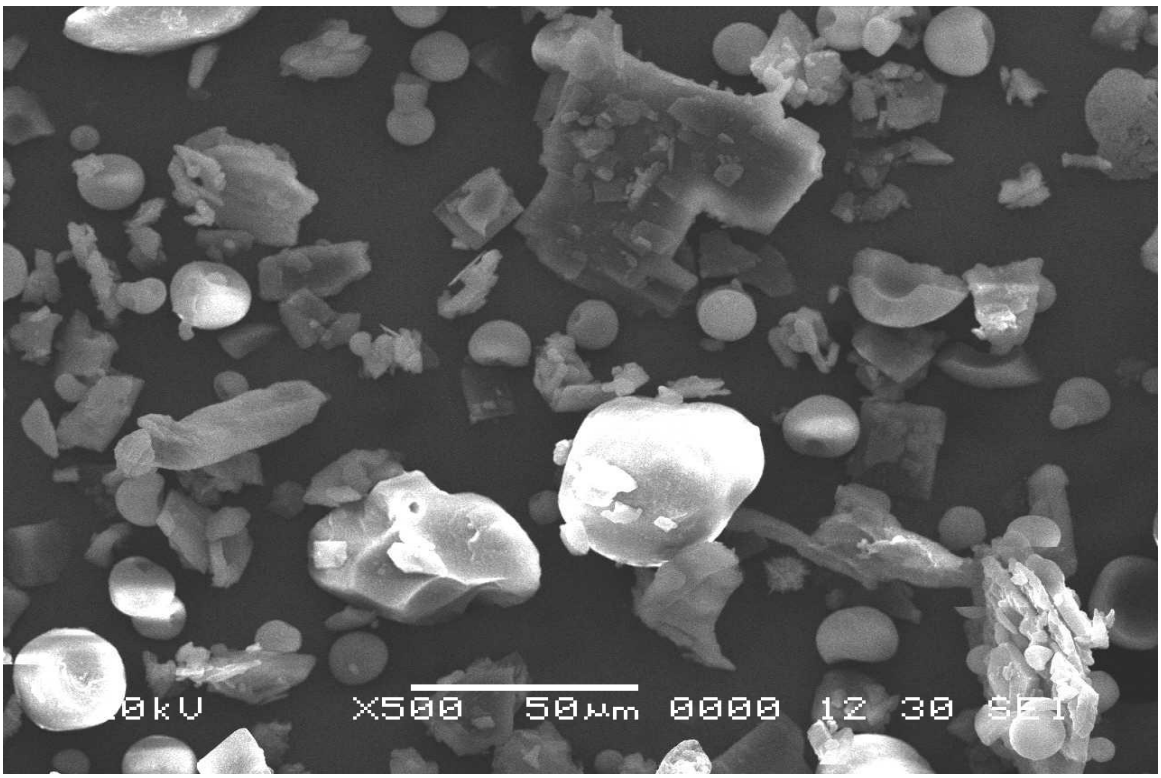


Figure No.1 Scanning electron micrograph of gelatin (type B) powder particles

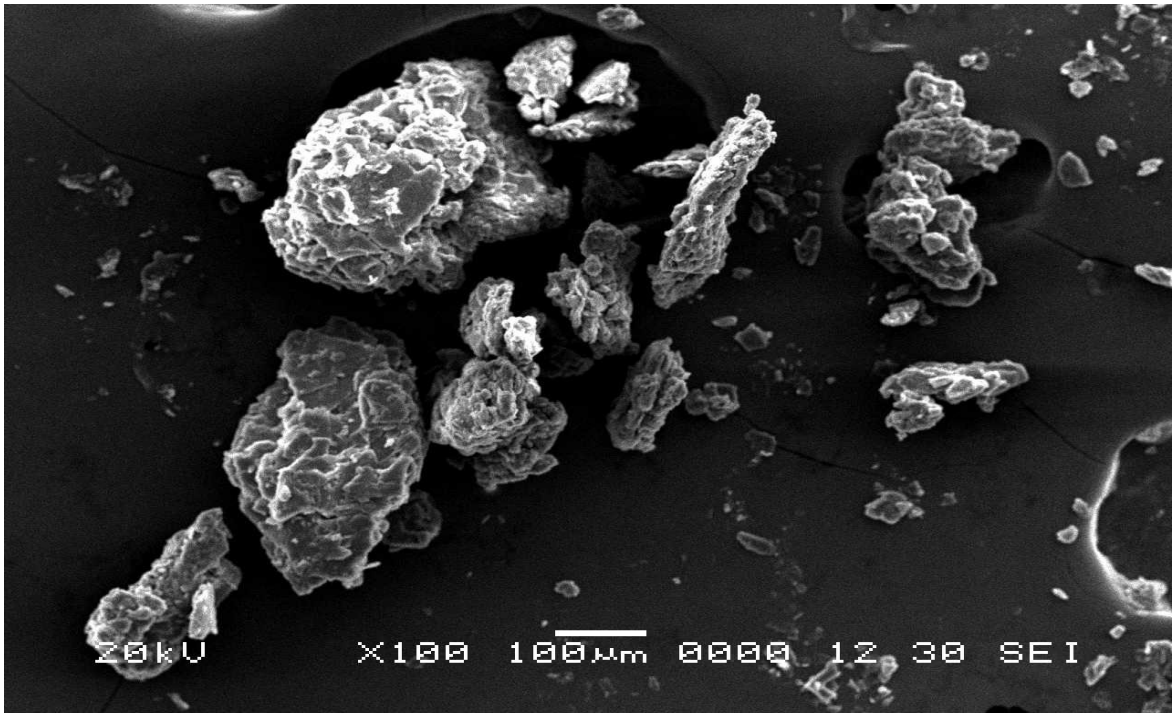


Figure No.2 Scanning electron micrograph of Fish gelatin powder particles

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Table No.2 Evaluation of Gelatin(Type-B) and Fish Gelatin:

Sr. No.	Parameters	Gelatin(Type-B)	Fish Gelatin
1	Bulk density (gm/cm^3)	0.597	0.139
2	Tapped density (gm/cm^3)	0.6819	0.6849
3	Hausners ratio	1.13	1.11
4	Compressibility Index	12.027%	10.863%
5	Angle of repose	48.140	45.109

Table No. 3 Loading and Evaluation of Propranolol HCL loaded Gelatin beads

Gelatin(Type-B)

Sr. No	Batches	% Entrapment efficiency	% yield	In vitro Drug Release
1.	A1	70.36	21.65	74.326
2.	A2	73.81	29.45	83.414
3.	A3	81.56	27.03	81.542
4.	A4	79.56	33.16	84.834
5.	A5	85.63	22.68	94.18
6.	A6	93.56	37.56	97.739
7.	A7	89.62	35.44	92.886
8.	A8	72.51	26.37	89.425
9.	A9	79.86	16.85	90.738
10.	A10	81.74	15.80	87.582
11.	A11	83.95	18.95	78.637

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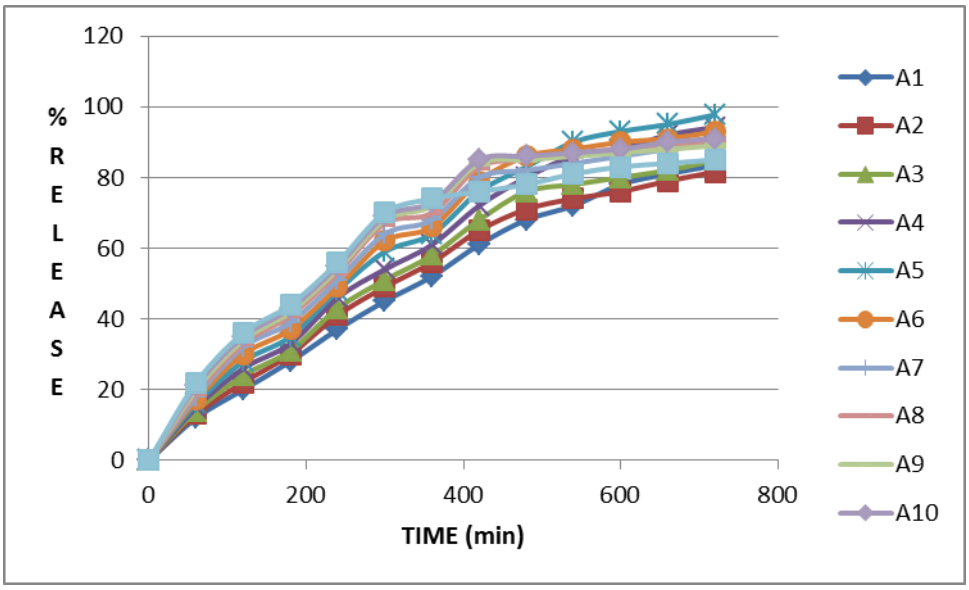


Figure No. 3 Cumulative % Drug release of preliminary batches

4. Conclusion

It is an evident from the overall studies that gelatin beads containing Propranolol HCL were prepared by emulsion cross linking method. Combination of both types of gelatin i.e gelatin (Type-B) and Fish gelatin resulted in the development of effective formulation. The formulation i.e gelatin beads so prepared could sustain the release of Propranolol HCL for significance of combination of different types of gelatins for sustained release of the drug.

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