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Development and Evaluation of Gelatin Microspheres of Tramadol Hydrochloride

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ABSTRACT

To develop formulations for effective management of chronic pain without side effects associated with NSAIDs and COX-2 antagonists, Tramadol hydrochloride, an opioid antagonist, was encapsulated within Gelatin microspheres for controlled delivery for longer periods. The microspheres were prepared using a single emulsion technique and were investigated. Tramadol hydrochloride could be encapsulated into Gelatin microspheres with an entrapment efficiency of 97.2%. Spherical, transparent, and free-flowing microspheres were obtained. Scanning electron microscopy revealed the spherical structures under the magnification of 200 µm. The FTIR and DSC analysis indicated the stability and compatibility of the drug in gelatin microspheres. The microspheres were in the suitable particle size range of 20 to 160 µm. The drug was released continuously for a period of 12 hrs with a maximum release of 99.79%.

Key words: Gelatin, microspheres, tramadol HCL, sesame oil

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INTRODUCTION

Effective management of chronic pain due to injuries or diseases is a great challenge experienced by Physicians. Non-steroidal anti-inflammatory drugs (NSAIDs), the most widely and commonly prescribed drugs, are associated with gastrointestinal, renal, and cardiovascular system (CVS)- related side effects. The consequences are dyspepsia in a large proportion of patients along with more serious adverse events such as upper gastrointestinal (GI) ulcers and bleeding.[1]

Although the next class of medications, COX-2 inhibitors, are gastro intestinally safer alternatives to NSAIDs, their use has other safety concerns shown by the withdrawal of Rofecoxib.[2] Like non selective NSAIDs, COX-2 specific inhibitors can also cause renal toxicity. Black box warnings have cautioned that the use of COX-2 inhibitors may be associated with GI and CVS risk.

In a survey conducted among 2,000 general practitioners in the UK to determine their prescribing patterns for analgesics in patients with osteoarthritis, the majority of physicians (69%) reported that their main therapeutic objective was to control pain without GI side effects.[3] At this juncture, Tramadol HCl is used as a choice of drug for the treatment of chronic pain without side effects associated with NSAIDS and COX-2 antagonists. Even though it belongs to a group of opioid antagonists, it acts as an effective analgesic without the risk of psychological dependence possessed by other opioid drugs.

Tramadol HCl is a synthetic opioid belonging to the amino cyclohexanol group. Chemically, it is (±)cis-2-

[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Tramadol Hydrochloride is a clinically effective, orally active, centrally acting analgesic. It can produce analgesia that has been compared with codeine or dextropropoxyphene. It has been used in the treatment of post-surgical pain, obstetric pain, cancer pain, and chronic pain of mechanical and neurogenic origin. The side effects of psychological dependence and euphoric effects are minimal. The patients initiated with tramadol CR reduced the number of NSAIDs rotations thereby producing earlier pain control. It has proved to be effective in the treatment of both experimental and clinical pain without causing serious cardiovascular or respiratory side effects.[4] The half-life of the drug is only about 5 hrs[4] and the usual dosage regimen is 50 to 100 mg every 4 to 6 hrs with a maximum dosage of 400 mg/day. The drug is freely soluble in water, hence, judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug. The predominant adverse effects of headache and nausea were reported more frequently by patients with Tramadol HCl Immediate release (IR) formulations. With the IR formulation, the incidence of headache and nausea was reported as 29% and 21%, respectively; while it was 18% and 11% with the sustained release (SR) formulations. Hence, a reduction in the frequency of administration improves patient compliance; a sustained release formulation of Tramadol HCl is desirable.[5] Therefore, the slow release formulation is an appropriate vehicle for chronic pain management.[6,7] The most commonly used method of modulating the drug release is to include it in a matrix system.[8] To achieve maximum therapeutic effect with a low risk of side effects, controlled release preparations in the form of microspheres have achieved successful results.[9] For drugs with higher water solubility, hydrophilic polymers are suitable as matrix agents to produce controlled drug delivery systems. The use of gelatin as a matrix forming agent has been investigated as a carrier to prepare microspheres of many drugs.[10,11] Gelatin is a non toxic biocompatible and biodegradable polymer. Therefore, to produce better formulations of drug for treating chronic pain with NSAIDSs sparing effect, the present work is aimed at the development of controlled release formulations of Tramadol HCL. The main objective is to formulate gelatin microspheres and characterize the *in vitro* drug release from Gelatin microspheres loaded with Tramadol HCl.

MATERIALS AND METHODS

A pure and certified sample of Tramadol HCL was given to us by M/s. Karnataka Antibiotics and Pharmaceuticals Ltd., Bangalore, India. Gelatin was purchased from Himedia Laboratories Pvt Ltd., Mumbai. Glutaraldehyde, toluene, and Isopropyl alcohol were purchased from SD Fine chemicals Ltd., Mumbai. All other chemicals and reagents were of analytical grade.

Preparation of microspheres: The microspheres were prepared according to the formula given in Table 1. A single emulsion technique was used to prepare the microspheres. A gelatin solution of various concentrations prepared in distilled water was used in the formulations. Different concentrations of glutaraldehyde were used to rigidize microspheres as shown in Table 1.

The gelatin solution was prepared in distilled water. The fine and size sieved (#100) powder of Tramadol HCl (100 mg) was added to it. The solution was homogenized using a magnetic stirrer. Sesame oil was then added gradually with continuous stirring maintained at 1000 rpm using an overhead stirrer. Then 30 ml of glutaraldehyde saturated toluene was added and stirred continuously for 4 hrs to allow the cross linking of gelatin microspheres. After rizidization, the encapsulated product was filtered and washed with cold isopropyl alcohol. Finally the product was dried at room temperature for 24 hrs.

Characterization of Microspheres

Entrapment efficiency: A small quantity of 50 mg of microspheres was taken and triturated with distilled water and transferred to a 50 ml standard flask. The volume was made up to 50 ml and mixed well. The solution was then kept aside for 12 hrs. After 12 hrs, the solution was made up to the volume with dissolution medium. It was then filtered and estimated for drug content by measuring the absorbance at 270 nm.

In vitro dissolution studies: In vitro dissolution studies were carried out for the microspheres using U.S.P Dissolution test apparatus-Model II (Electro lab, India). The study was carried out using 900 ml of distilled water as dissolution medium maintained at a constant temperature of 37±2°C

Table 1: Formulations of microspheres

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Tramadol HCl, mg	100	100	100	100	100	100	100
Gelatin, 20 ml	5%	5%	4.5%	4%	3.8%	3.7%	3.65%
Sesame oil, ml	50	50	50	50	50	50	50
Glutaraldehyde,mg	15	20	22	25	25	25	25

and subjected to a stirring speed of 50 rpm. Accurately weighed microspheres equivalent to contain 50 mg of drug were placed in the medium and the release was studied. The percent of drug dissolved was estimated in 5 ml aliquot samples and was withdrawn at an interval of 30 min for the first 4 hrs and at 1 hr intervals up to 12 hrs. The samples withdrawn at every interval were replaced immediately by fresh distilled water to maintain sink conditions. The samples were filtered though 0.45 µm Millipore filter paper and estimated for Tramadol HCl content by measuring absorbance in a UV-visible spectrophotometer at λ_{max} of 270 nm against a solvent blank. The dissolution profiles are shown in Figure 1.

Microsphere Morphology and Surface Characteristics: The microsphere shape and morphology of the selected microspheres was investigated using Scanning Electron Microscopy (JEOL, JSM-6360) at 10 KV. Prior to examination, the samples were gold coated under vacuum (Fine coat, Ion Sputter, JFC-1100) to render them electrically conductive. The photographs of pure drug and selected microspheres (F-7) are presented in Figure 2.

Particle size analysis: Particle size analysis was carried out using the optical microscopic method with the help of a calibrated eye piece micrometer. The size of around 300 particles was measured and an average diameter was calculated**.**

Fourier Transform Infrared Spectroscopy: Fourier Transform Infrared Spectroscopy (FTIR) spectra were recorded for pure tram on samples prepared in Potassium bromide disks using a Thermo Electron IR spectrophotometer. Samples were prepared in potassium bromide disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1} and represented as % transmittance *vs.* wave number. An IR spectroscopy has been used to determine the quantity of the interaction between the drug and the carrier.

Diffrenctial Scanning Calorimetry: Differential Scanning Calorimetry (DSC) of pure tramadol HCl and selected Gelatin microspheres of Tramadol HCl was conducted using a TAQ 1000 Thermal analyzer at a scanning range of 10^0c/min in the temperature range of 30° to 240°c under static air atmosphere.

Release Kinetics: To determine the order of drug release from microspheres, the dissolution data was fitted into zero-order, first order, and Higuchi equation. The dissolution data was also fitted in an exponential equation (korsmeyer-Peppas) often used to describe drug release behavior from polymeric systems when the mechanism is not well known or when more than one type of release phenomenon is involved.

RESULTS AND DISCUSSION

In the first formulation F-1, the microspheres were not clearly produced when the concentration of gelatin was 5% and the gluteraldehyde concentration was 15 mg. In the rest of the formulations, the concentration of gelatin was gradually reduced and the concentration of gluteraldehyde was increased to 25 mg. The microspheres were obtained in all the formulations and were evaluated for particle size analysis, entrapment efficiency, and *in vitro* dissolution. The results are given in the Table 2.

In the formulation F-2, the microspheres were produced with a particle size range of 100 to 140 um. The drug entrapment was 14.9% and there was a burst release in 1 hour. In case of formulation F-3, the concentration of gelatin was reduced to 4.5%, and the microspheres were obtained in the particle range of 80 -120, entrapment

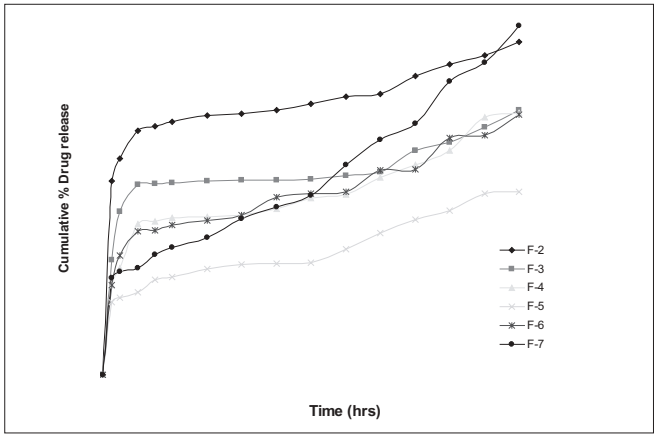

Figure 1: Dissolution profiles of prepared microspheres

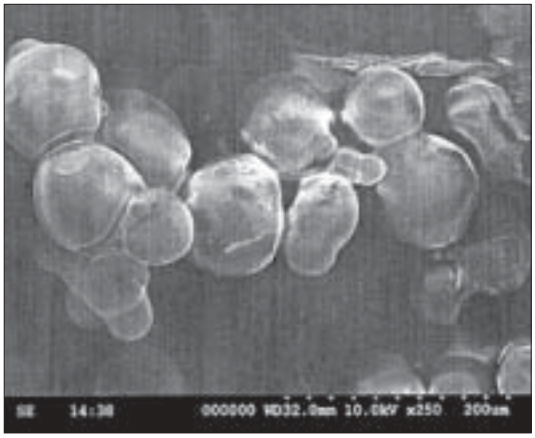

Figure 2: SEM photograph of selected microspheres under magnification 200 µm

Table 2: Evaluation parameters of prepared microspheres

Formulation	Entrapment efficiency (%)	Cumulative % drug release at 12 hrs	Particle size range
F-2	14.9	88.5	100-140
F-3	40.3	70.3	80-120
F-4	68.7	69.7	80-100
F-5	97.6	75	40-80
F-6	95	69.3	22-60
F-7	91.26	96	20-40

efficiency was increased to 40.3%. The drug release was only 70.3% after 12 hours. In case of formulation F-4, the gelatin concentration was reduced to 4%. The microspheres were produced with a particle size range of 80-100 μm and an entrapment efficiency of 68.7%. There was a burst release of 30% in the first 1 hr and only 69.7% of the drug was released after 12 hrs. In next formulation F-5, the polymer concentration was decreased to 3.8% and the microspheres were produced in the particle range of 40-80 um with the entrapment efficiency increased to 97.6%. But the release of drug was only 75% in 12 hours with comparatively less of a burst release than the previous formulation i.e., 50.6% in one hour. Formulation F-6 was made with 3.7% gelatin solution. The particle size range of the microspheres was 22-60 um and the entrapment efficiency was 95%. To improve the drug release at the 12^{th} hour, the next formulation F-7 was prepared by using 3.65% gelatin solution. The spherical microspheres were produced with the particle range of 20-40 um and the entrapment efficiency of 91.26%. The dissolution pattern of F-7 indicated studies ideal controlled release pattern of less than 20% in the first 1 hr and 96% of drug release after 12 hrs.

Hence, formulation F-7 was considered as a promising formulation and it was subjected to further studies such as scanning electron microscopy (SEM), FTIR, and DSC. SEM studies revealed discrete spherical structures of microspheres as shown in Figure 2. Sieve analysis data indicated the optimum particle size range of formulations F-2 to F-7.

FTIR spectra of pure drug and microspheres of Tamadol HCl revealed its principal peaks of amine stretch at 1356 cm^{-1} and –OH stretch at 3304 cm^{-1}. The IR spectrum microspheres of Tamadol HCl also presented all the peak characteristics of pure drug indicating no interaction between the drug and Gelatin.

DSC thermograms of pure Tramadol HCl and microspheres of Tamadol HCl indicated their endothermic peaks at 177.78°C. and at 178°C, respectively. These values indicated the absence of drug to polymer interactions.

The drug release kinetic studies evaluated by zero-order, first order, and Higuchi plots indicated that the release is apparently zero order as the regression value was closer to unity in case of zero order plot (R= 0.968). The correlation coefficients obtained for the Higuchi plot (R = 0.96) was found to be superior on comparison with r values of the Korsmeyer-Peppas plot (R = 0.584) indicating that the mechanism of drug release from Tramadol HCl microspheres was diffusion controlled.

CONCLUSION

Tramadol HCl can be developed successfully as a controlled drug delivery system in the form of Gelatin microspheres. The Gelatin microspheres can be prepared by using the single emulsion technique. This formulation can be a choice of treatment for management of chronic pain with much more patient comfort without side effects.

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