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ABSTRACT SUMMARY
The goal of the proposed research is to develop microparticle (MP)-based sustained release formulations for the treatment of psychostimulant addiction and relapse, based on the FDA-approved partial κ/μ opioid agonist nalbuphine. In this study, PLGA was used as a matrix material to develop and characterize MPs as a controlled drug delivery system. The effects of different formulation variables on the properties of nalbuphine MPs prepared by double emulsion technique were investigated.

INTRODUCTION
Nalbuphine HCl is a semisynthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is morphine-like, with partial agonist activity at the κ-opiate receptor and antagonist activity at the μ-opiate receptor.1 It acts by blocking/attenuating and reversing physical effects of narcotic drugs, thus leading towards effective management of opium dependence. The recommended injection dose is 40-80 mg daily for a 70 kg adult. Since nalbuphine HCl has short elimination half-life (about 5 h when injected in saline) and poor oral bioavailability, frequent injection (e.g. every 3-4 h) are often needed. Microparticles of biodegradable and biocompatible polymers that can be administered intramuscularly (i.m.) could be promising carriers for delivery of nalbuphine HCl as an alternative delivery route that would decrease the required drug dosage by virtue of controlled constant drug release.2 Patient compliance and therapeutic effectiveness may thus be improved by prolonging blood drug concentration, therefore eliminating the need for frequent injections. Also, depot dosage forms are desirable due to treatment adherence issues. The objectives of this study were: (i) to develop naltrexone HCl (model drug, initially used as proof of principle)-loaded MPs by water1/oil/water2 (W1/O/W2) double emulsion-solvent evaporation method using dichloromethane (DCM) as the solvent, (ii) characterize naltrexone HCl-loaded MPs with respect to particle size, encapsulation efficiency (EE), drug loading and morphology, (iii) determine the influence of the concentration of polymer and polyvinyl alcohol (PVA) on the particle size of the MPs, (iv) study the effect of various formulation variables: polymer concentration, amount of surfactant (PVA), organic solvents, volume of the external water phase and additives, on EE and drug loading, (v) use the optimized formulation parameters for the fabrication of nalbuphine HCl MPs, and (vi) study the in vitro release behavior of nalbuphine HCl from MPs in phosphate buffer.

EXPERIMENTAL METHODS
The MPs were prepared using a water-in-oil-in-water double emulsification method. Briefly, the drug was dissolved in PVA solution (in water, internal water phase (W1)). This was emulsified into the polymer solution (in DCM, oil phase (O)) by sonication (30 sec) to form the first emulsion (W1/O) and was immediately added to PVA solution (in water, external water phase (W2)) and homogenized at 9500 rpm (30 sec) to form the second emulsion (W1/O/W2). The emulsion was then stirred enough to allow the evaporation of DCM. The particles were collected by centrifugation at 4500 x g for 10 min, washed twice with water and freeze-dried for 48 h. The influence of various formulation variables, namely, the polymer concentration, amount of surfactant, organic solvents, volume of the external water phase and different additives, on the MP properties was analyzed.
The surface morphology of resulting MPs was examined by scanning electron microscopy (SEM). The formulation was characterized for particle size, drug EE and drug loading. The in vitro drug release from MPs was carried out in pH 7.4 (physiological) buffer at 37 °C.

\[ \text{EE (\%)} = \frac{\text{Drug entrapped in MPs (mg)}}{\text{Initial amount of drug added (mg)}} \times 100 \]

Drug loading = µg of drug/mg of MPs

RESULTS AND DISCUSSION
The highest EE and loading for nalbuphine HCl MPs were obtained with 0.02 M Tris buffer system at pH 8 in W_2 phase. This may be due to the less soluble nonionic state of the drug at this pH. Tris also increases the diffusional resistance to the drug to the W_2 phase. The particles formed were monodisperse with spherical and smooth morphology. However, in the presence of Tris, particles were porous. The EE and particle size of MPs increased with increasing amounts of polymer in DCM due to the increased viscosity of the O phase. This reduces the stirring efficiency and shear stress, causes droplet aggregation, thus forming larger particles. It also prevents the leakage of W_1 through O into W_2. Similar results were observed on increasing PVA amounts in W_1 and W_2 phases (Figure 1). For nalbuphine HCl, an EE of 27.5 % and loading of 6.9 µg of drug/mg of MPs was obtained with the optimized parameters.

CONCLUSION
Microparticles containing nalbuphine HCl loaded in PLGA matrix were successfully developed with particle size distribution suitable for i.m. injection. The particle size, encapsulation efficiency and loading were found to be affected by the polymer and PVA amounts.

REFERENCES

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