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Short Communication

Development of Solid Lipid Nanoparticles of Lamivudine for Brain Targeting

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Abstract
The objective of present investigation was to enhance brain penetration of Lamivudine, one of the most widely used drugs for the treatment of AIDS. This was achieved through incorporating the drug into solid lipid nanoparticles (SLN) prepared by using emulsion solvent diffusion technique. The formulations were characterized for surface morphology, size and size distribution, percent drug entrapment and drug release. The optimum rotation speed, resulting into better drug entrapment and percent yield, was in the range of 1000-1250 r/min. *In vitro* cumulative % drug release from optimized SLN formulation was found 40-50 % in PBS (pH-7.4) and SGF (pH-1.2) respectively for 10 h. After 24 h more than 65 % of the drug was released from all formulations in both mediums meeting the requirement for drug delivery for prolong period of time.

Keywords: Emulsion solvent diffusion method, Polydispersity index, Blood brain barrier (BBB).Zeta potential.

INTRODUCTION

AIDS is a pernicious virally mediated disorder, the prognosis of which is usually death Antiviral agents must therefore gain access to the central nervous system (CNS) in therapeutically relevant concentrations if AIDS dementia is to be adequately treated. Such pharmacokinetic considerations are often not met because of the ostensibly protective blood-brain barrier (BBB) which effectively prevents or reduces the entry of many hydrophilic drugs, including antiviral ribosides P. Hence, the targeting of these drugs is important. Such targeting is carried out mainly by Chemical Drug Delivery System (DDS) i.e. 1, 4-dihydropyrimidine system but this system dissociates rapidly hence not much effective. Another approach was nanoparticulate carriers are also investigated but these nanoparticulate carriers are rapidly cleared by mononuclear phagocyte system (MPS) hence, the concentration of the drug in the brain is not sufficient. Recently, increasing attention has been focused on solid lipid Nanoparticles (SLN), because it offers following advantages- possibility of controlled drug release [1,2] and drug targeting, increased drug stability, high drug payload, no biotoxicity of the carriers, avoidance of organic solvents, no problems with respect to large scale production, cost effective and sterilization.

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Furthermore, the incorporation of hydrophilic Lamivudine in SLN carriers results in decrease bone marrow toxicity, increased bioavailability and enhanced antiviral activity.

MATERIALS AND METHODS

Materials

Stearic acid and PVA were supplied from Central Drug House, Delhi. The drug Lamivudine was supplied from the Ranbaxy Laboratories Limited, Dewas (M.P.).The solvents (acetone, ethanol) of analytical grade were purchased from SD Fine Chemicals, Mumbai.

Preparation of Solid Lipid Nanoparticles

In the present study SLN were formulated employing emulsion solvent diffusion technique[3].Briefly, the weighed amount of stearic acid and the weighed drug (Lamivudine) were dissolved completely in a mixture of (12 ml) and (12 ml) in water at 50 °C. The resultant organic solution was poured into the acidic aqueous phase containing 1% PVA (w/v) under mechanical agitate with 500-1000 r/min at 4-8 °C for 15 min. The pH value of the acidic aqueous phase was adjusted to 1.10 by addition of 0.1 M hydrochloric acid. The SLN suspension was quickly produced. The entire dispersed system was then centrifuged at 8000 r/min for 30 min and re-suspended in distilled water. The resultant dispersion was dried by lyophilization.

Characterization of SLNs

Size and Size Distribution (Polydispersity Index) and Measurement of Zeta Potential

The particle size, size distribution and zeta potential of solid lipid nanoparticles were determined by photon correlation spectroscopy (PCS) using Zetasizer 3000 HS (Malvern

Table 1 Effect of Lipid Concentration

Formulation (s) code	D:L ratio	Encapsulation Efficiency (%)	Percentage Yield (%)
S1	1:0.5	58.50	68.85
S 2	1:1	72.47	74.50
S 3	1:1.5	72.21	76.88
S 4	1:2	72.15	71.90
S 5	1:2.5	71.96	67.66

Table 2: Effect of Stirring Rate

Formulation(s) code	Stirring Rate	Encapsulation Efficiency (%)	Percentage Yield (%)
SR1	500	72.51	73.67
SR2	750	73.05	79.10
SR3	1000	75.43	79.97
SR4	1250	75.19	79.35

Table 3. Effect of Temperature

Formulation(s) code	Temp. (°C)	Encapsulation Efficiency (%)	Percentage Yield (%)
T1	40	70.40	75.20
T2	50	76.21	81.11
T3	60	69.55	71.32
T4	70	67.15	69.55

Instrument Ltd UK) [4].

Surface Morphology

The surface morphology and structure were visualized by scanning electron microscopy (JEOL JSM-6400 UK).

Percent Drug entrapment

The percent drug entrapment was determined using following equation

$$\%\ \text{Drug entrapment} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulation}} X100$$

Percentage yield

After freeze drying of SLN, the SLN obtained were collected and weighted accurately. The percent yield of solid lipid nanoparticles was calculated

Optimization of Process Variables

The preparation of Solid Lipid Nanoparticles involves various process variables like concentration of drug, lipid and surfactant, temperature and agitation rate. The effect of above variables was observed on the particle size, encapsulation efficiency, percentage yield of Solid Lipid Nanoparticles.

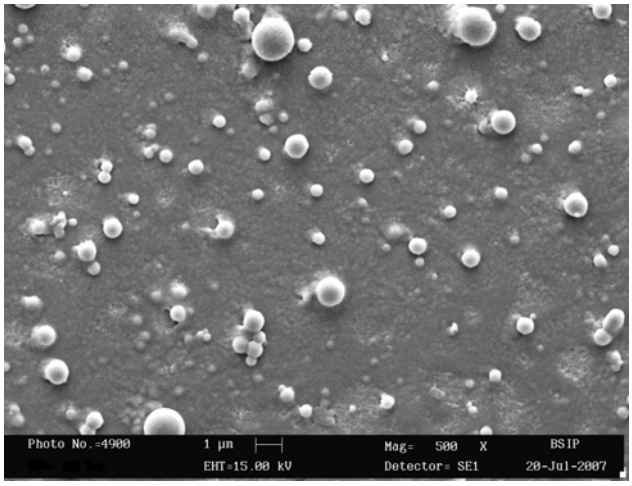
***In vitro* Release Rate Studies**

The drug release studies of SLN were carried out by the dialysis cell membrane method [5].*In vitro* drug release of Lamivudine from Solid Lipid Nanoparticles was estimated in PBS (pH 7.4) and SGF (pH 1.2) at 37°C for 24 h under sink condition.

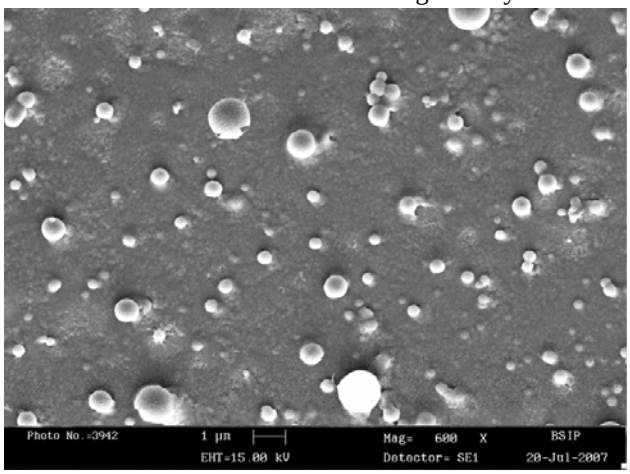
Results and Discussion

The Solid Lipid Nanoparticles were prepared by emulsion solvent diffusion method. The scanning electron microscopy SEM) photographs revealed smooth texture of formulated SLNs (figure 1). Under the lower pH condition (pH 1.10), the zeta potential of system was more nearly zero and produced aggregation of the SLN and then the separation of SLN from suspension is easily operated by centrifugation. In case of SLN, on increasing the concentration of lipid, the amount of drug entrapment increased up to certain extent and then there was no effect of lipid concentration on drug entrapment. The maximum % drug entrapment was 72.47 % in S2 1:1 and. This was due to availability of optimum concentration lipid for drug entrapment. Less drug entrapment found was 58.50 % in S1 where the drug lipid ratio is 1:0.5. After that there was no considerable effect on drug entrapment due to saturation of lipid. On raising the concentration of lipid, the increase in % yield of Solid Lipid Nanoparticles was observed like 68.85, 74.50, 76.88, 71.90 and 67.66 for formulation S1, S2, S3, S4 and S5 respectively (Table 1). As drug concentration increased % yield was also increased up to certain extent due to availability of optimum concentration of solvent for dispersion of lipid and then decreases due to lack of solvent for dispersion of lipid. On increasing the stirring rate the increase in % yield was observed. It was 73.67, 79.10, 79.97 and 79.35 % for formulation P1, P2, P3 and P4, respectively.

This indicates that further increase in stirring rate from 1000 to 2000 r/min was not affecting the % yield of Solid



A.



B.

Figure1. SEM images of SLNs- A) Formulation V_1 B) Formulation V_2

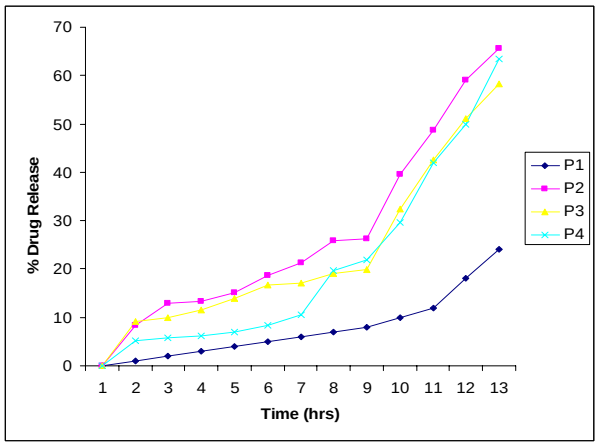


Figure 2. *In Vitro* Drug Release Profile of Lamivudine from Solid Lipid Nanoparticles in PBS (pH 7.4) at 37°± 1°C

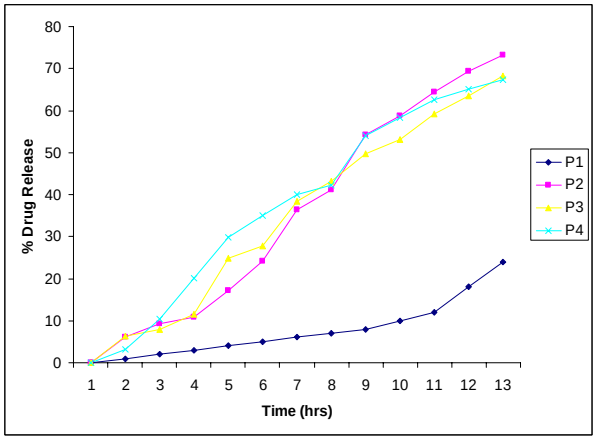


Figure 3. *In Vitro* Drug Release Profile of Lamivudine from Solid Lipid Nanoparticles in SGF (pH 1.2) at 37°± 1°C

Lipid Nanoparticles (Table 2).

There is definite effect of varying the temperature on the drug entrapment of SLNs. On rising the temperature from 40° C to70 °C, firstly increase in drug entrapment takes place due to increase in melt viscosity of lipid and then drug entrapment decreases due to crystallization of the lipid. Also at higher temperature the solvent get evaporated instantly due to which drug and lipid gets precipitate affecting the % yield of Solid Lipid Nanoparticles (Table 3). *In vitro* drug release of Lamivudine from Solid Lipid Nanoparticles was estimated in PBS (pH 7.4) and SGF (pH 1.2) at 37°C for 24 h under sink condition. It was observed that on increasing the concentration of lipid the rate of release of drug from Solid Lipid Nanoparticles decreased, because the thickness of polymer was increased and diffusion distance for drug to diffuse out from Solid Lipid Nanoparticles was increased. The observations were made for continuous10h. The smaller Nanoparticles released the drug more rapidly than larger ones in the media PBS (pH 7.4) and SGF (pH 1.2) at the initial stage. The drug release rate could be controlled by the lipid concentration. In general, the faster release was obtained with the smaller devices, which possess the large surface area. As apparent figure 2 and 3, there is steady and sustained release of drug from SLN. This work can further be extended in the area of *in vivo* studies. The various combinations are used for Anti-HIV therapy hence these combinations can also be incorporated in the Stearic Acid SLN. Further the present SLN can be molded in desirable dosage form. Another area where this work can be extended is comparison of various approaches of brain targeting with SLN. This will give more idea about the targeting potential of SLN or we may synthesize the prodrug of anti-HIV drug and incorporating it into SLN.

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