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Research Article

Cavinton - Loaded Solid Lipid Nanoparticles: Design and Characterization

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Abstract

Solid lipid nanoparticles (SLNs) are novel colloidal particles for oral delivery with enhanced absorption rate. They overcome the disadvantages of other colloidal carriers such as emulsion, liposome, and polymeric nanoparticles. Cavinton is unique memory enhancer drug with short half-life and variable oral bioavailability (6-60%). In market, Cavinton is available as 5mg tablet thrice a day. The aim of the study was to develop controlled release SLNs by incorporating this drug in to lipid nanocarriers where nanosize particles and lipid used for formulation would help to control drug release over prolonged period. SLNs were prepared by High shear homogenization (HSH) technique using stearic acid as solid lipid core, Tween 80 and Poloxamer 188 as stabilizers. Formulations were optimized by 3² factorial design approach. Particle size and its distribution were determined by Malvern Mastersizer and found to be 400 nm with polydispersity index 0.28. Transmission Electron Microscopy (TEM) shown that SLNs were uniform spherical in shape. In vitro release studies shown that SLNs dispersions were able to control the drug release and it followed diffusion controlled release mechanism. The palatability of nanodispersion was improved using sweetener and flavors. HSH was found to be effective method to prepare high quality SLNs for once day oral administration of Cavinton.

1. INTRODUCTION

Drug carriers of sub micron sizes are attracting more attention now a day. Because of their small size they exhibit distinctive properties, which may enable drug release to be controlled and sustained^{1,2}. Particulate drug carriers investigated for many years include oil-in-water emulsions, liposomes, microparticles and nanoparticles based on synthetic polymers or natural macromolecules. The scarcity of safe polymers with regulatory approval and their high cost have limited, the wide spread application of polymeric nanoparticles to clinical medicine. To overcome the problems of polymeric nanoparticles, solid lipids have been put forward as alternative carriers, in particular lipophilic pharmaceuticals³. Successful implementation of lipid particles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the micro or nanometer size⁴. Solid lipid particles are micro- and nano-scale drug carriers possessing matrix made from fatty acid, glyceride, fatty alcohol and solid wax with high melting points. The SLNs are composed of physiological lipid, dispersed in water in an aqueous surfactant solution.

For lipophilic drugs, they offer higher loading capacity compared to the polymeric nanoparticles⁵. SLNs are poised to open new avenues in research and therapy. In addition, nanotechnology offers a means of providing novel formulation for existing marketed drugs as a way of extending the patent lifetime and therefore the exclusivity in terms of sales⁶. The rationale for oral controlled drug delivery is to alter the pharmacokinetics of pharmacological active moieties by using novel drug delivery systems.

Cavinton is unique memory enhancer drug, which increases cerebral metabolism by increasing glucose and oxygen utilization.

Cavinton has half-life 2.5 ± 0.48 hours⁷. However, Cavinton is insoluble in water and suffers from low oral bioavailability. In market Cavinton is available as 5 mg tablet thrice a day. Therefore to reduce dosing frequency and to improve drug release, the present study was undertaken to develop controlled release Cavinton loaded solid lipid nanoparticles for oral administration. Solid lipid nanoparticles (SLNs) can be used to improve oral bioavailability of poorly soluble drugs⁸. This investigation consists of preparation, optimization, and evaluation of Cavinton loaded solid lipid nanoparticles, and preparation of palatable, aesthetic solid lipid nanoparticles dispersion for oral delivery systems.

2. MATERIALS AND METHODS

2.1 Materials

Cavinton was obtained as gift sample from Themis Medicare (Mumbai, India). Stearic acid was provided by Signet chemicals, (Mumbai, India). Poloxamer 188 was obtained from BASF, (Mumbai, India). All other chemicals and solvents used were of analytical reagent grade.

2.2 Preparation of Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLNs) were prepared by High shear homogenization (HSH) technique. The formulation was optimized by 3² factorial design approaches (Fig. 1a, 1b and 1c).

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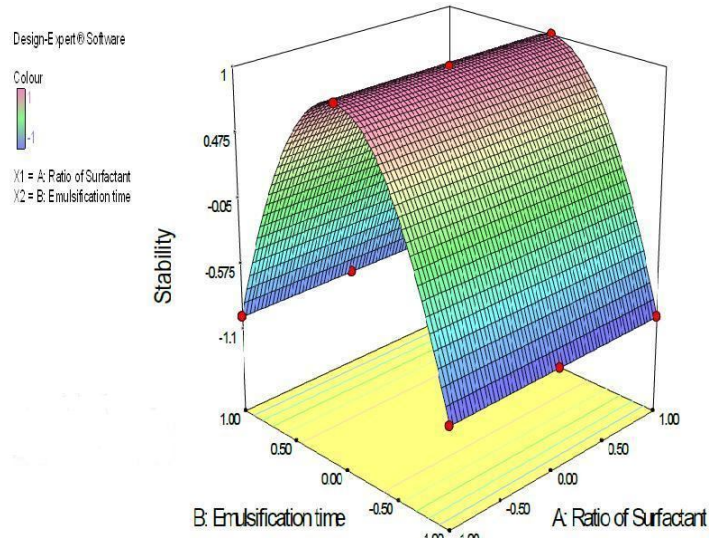


Fig.1a: Effect of emulsification time and different ratios of surfactants on stability

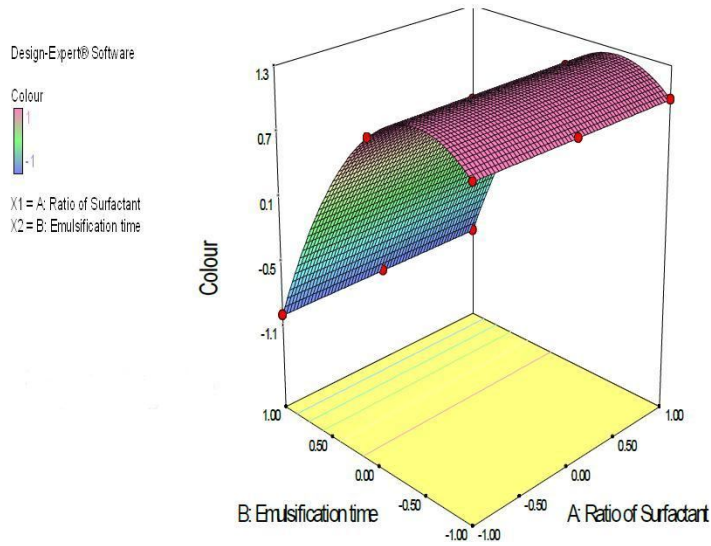


Fig.1 b: Effect of emulsification time and different ratios of surfactants on colour

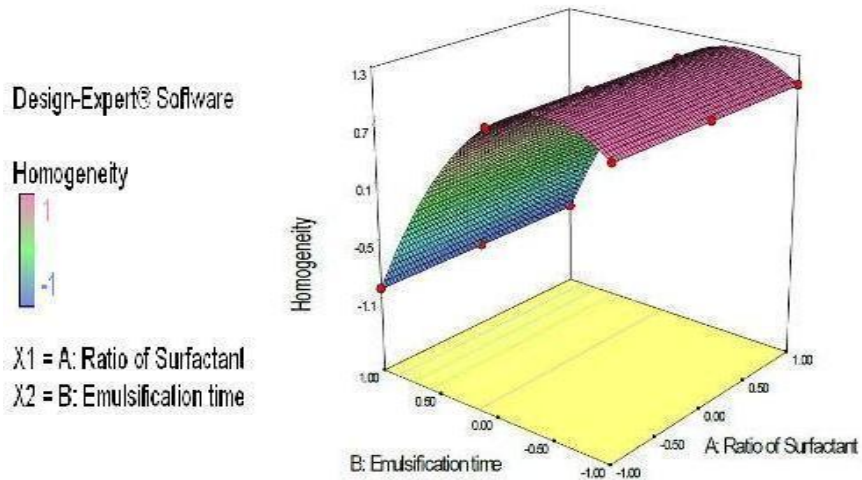


Fig.1 c: Effect of emulsification time and different ratios of surfactants on Homogeneity

Stearic acid (3g) was melted 5-10°C above the melting point of lipid. Drug was dissolved in acetone (2 ml) and dispersed in the lipid melt. Tween 80 and Poloxamer 188 were dissolved in 100g water to the same temperature of lipid melt. Hot aqueous surfactants solution was added to drug-loaded lipid to the same temperature by high speed stirring using ultra-turrax 725 (IKA-Werke, Staufen, Germany) with emulsification time 10 min to 45 mins. This dispersion was then subjected to high pressure homogenization using APV 2000 (Invensys, Copenhagen, Denmark) homogenizer at 1000 bars. The obtained nanodispersion was allowed to cool to room temperature, forming lipid nanoparticles by recrystallization of the dispersed lipid.

2.3 Preparation of Palatable Nanoparticles Dispersion

The optimized formulation of SLNs dispersion was made palatable by incorporating Acesulfame K sweetener and flavours. Formulations with varying concentrations of Acesulfame K 0.1%-1% were prepared. Flavours like vanilla, orange, and black currant were tried out.

2.4 Characterization and Evaluation of Solid Lipid Nanoparticles

The Solid Lipid Nanoparticles were characterized for following parameters:

2.4.1 Physicochemical Properties

The nanoparticulate dispersion was characterized for physicochemical properties such as color, odor, pH and taste over a period of 48 hours of undisturbed standing.

2.4.2 Particle Size and Size Distribution

Particle size analysis of the selected formulation was performed using Malvern Mastersizer 2000 (Malvern Instruments, Worcestershire, UK) and theory used was laser diffraction with beam length 2.40 mm, range lens of 300 RF mm, and at 14.4% obscuration. It is shown in figure 2.

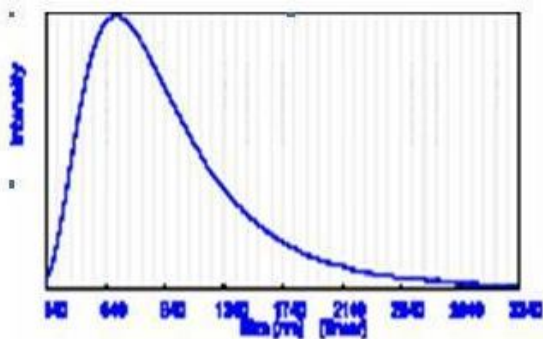


Fig.2: Particle size analysis

2.4.3 Transmission Electron Microscopy (TEM)

TEM was performed using JEOL 1010 (JEOL Ltd. Tokyo, Japan). One drop of nanoparticulate dispersion was placed on the grid, dried for 3 to 5 minutes, and drained on the filter paper. The grid was further dried by keeping it in the Petri plate; then it was loaded in the transmission electron microscope and an area was scanned for observation of nanoparticles.

2.4.4 Total Drug Content

Drug content was determined by developed validated UV-visible analytical method. SLNs dispersion (20 gm) was extracted with 100 ml ethanol under ultrasonication for 15 mins. After filtration and dilution, amount of drug was determined using Jasco UV-visible spectrometer at 274 nm (Jasco, Inc, Easton, MD).

2.4.5 In vitro Drug Release Studies

In vitro drug release studies were performed with USP XXII apparatus type 1 containing 900 mL 0.1N HCl and pH 6.8 Phosphate buffer as dissolution media. A predetermined amount of Cavinton loaded SLNs dispersion was poured into the cellophane bag with the two ends fixed. The assembly was stirred at a speed of 100 rpm at 37°C. Samples were collected over period of 24 hours and analyzed using Jasco UV-visible spectrometer at 268 nm.

2.4.6 Stability Studies of Cavinton in Solid Lipid Nanoparticles (SLNs)

The developed solid lipid dispersion was subjected to stability studies at various temperature and humidity conditions as per ICH guidelines. The samples were withdrawn at monthly intervals and effect of storage conditions was observed on physicochemical characteristics, particle size and *in vitro* release profiles of SLNs dispersion.

3. RESULTS

3.1 Physicochemical Properties

The nanoparticulate dispersion was milky white in color, odorless, and fluid in nature. The pH of the dispersion was in the range of 5.4 to 5.9. Formulation containing 1% Acesulfame K and black currant as flavour gave aesthetic SLNs dispersion with pleasant sweet taste.

3.2 Particle Size and Size Distribution

The particle size analysis of the nanoparticulate dispersion by laser diffraction using Malvern Mastersizer showed particle size ranging approximately from 300 nm to 900 nm. The nanoparticulate dispersion containing Tween 80: Poloxamer 188 (1:1) showed a relatively smaller particle size (400nm) with polydispersity index 0.28.

3.3 Transmission Electron Microscopy

TEM study of nanoparticulate dispersion (Fig.3) indicated that the spherical shape of nanoparticles entrapping the drug Cavinton.

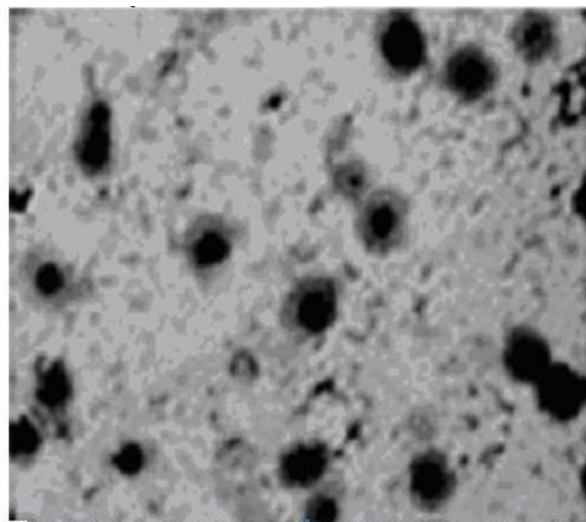


Fig.3: TEM of nanoparticulate dispersion

3.4 Drug Content

Drug assayed showed 98% to 100% contents of labeled amount.

3.5 In vitro Release Studies

The results of *in vitro* release studies shown that ratio of surfactants had the most pronounced effect on burst release from SLNs formulations. A Poloxamer 188 to Tween 80 ratio of 1:1 was found to be most effective to develop SLNs particles. The higher correlation coefficient with Higuchi model indicates that drug release from the SLNs formulations followed diffusion controlled mechanism.

3.5 Physical Stability of SLNs Dispersion

SLNs dispersion did not show changes in properties when maintained at 4°C. In contrast SLNs dispersion formed gel and yellow color within one month when stored at 25°C and 40°C. This may be due to the gel formation tendency of the solid lipid core. It was also recorded a similar gel-forming tendency of dispersion prepared with sub-optimized composition.

4. DISCUSSION

Solid lipid nanoparticle dispersion was prepared by high shear homogenization technique and formulations were optimized using 3² factorial design approach. Factorial design was used to study the effect of simultaneously varying any two independent variables such as ratios of surfactants and emulsification time on particle size, stability of the SLNs dispersions as dependent variables. Blackish emulsion was obtained after 45 min. of emulsification times. Formulations with 25 min. emulsification time exhibited desired physical appearance and no phase separation. Surface-Response diagrams had shown the effect of emulsification time on the colour, homogeneity and stability of the formulations. Thus the optimum emulsification time was 25 mins. Ratio of emulsifying agent has not significant effect on emulsion properties.

Homogenization at pressure lower than 800 bars did not result in achievement of all the particles in the submicron range. Homogenization pressure 1000 bars result in colloidal dispersion.

Preparation was made palatable with Acesulfame K, as it is a calorie-free sweetener 200 times sweeter than sugar.

The results of *in vitro* release studies shown that ratio of surfactants had the most pronounced effect on burst release from SLNs formulations. A Poloxamer 188 to Tween 80 ratio of 1:1 was found to be most effective to develop SLNs particles.

Burst release may be due to stronger solubilization effect of Tween 80 as compared to Poloxamer. From this result, we concluded that the surfactants made an important contribution to the difference between burst release from the developed formulations. This finding may be due to presence of Tween 80 at high level. This leads to an increase in solubility of drug in aqueous phase and provides burst release. This finding was in agreement with Muller, (2000), who proved that the amount of drug partitioning to the water phase would increase with increasing hydrophilic surfactant concentration.

The Result indicates that the rate controlling stage in the release process was diffusion of drug from nanoparticles to the external medium. Thus, *In vitro* release studies showed that the SLNs dispersions were able to control the drug release and it followed diffusion controlled release mechanism.

The results of stability study indicated that there was acceptable particle size, drug release profile and future clinical use of generated dispersion will require that they should be stored and maintained at refrigerated conditions.

5. CONCLUSION

Solid lipid nanoparticle dispersion was prepared by high shear homogenization technique and formulations were optimized using 3² factorial design approach. Nanoparticulate dispersion had shown a relatively smaller particle size with polydispersity index 0.28. In TEM study spherical shape nanoparticles were observed. The higher correlation coefficient with Higuchi model indicates that drug release from the SLNs formulations followed diffusion controlled mechanism. The results of stability study indicated that, there was acceptable particle size, drug release profile. Future clinical use of generated dispersion will require that, they should be stored and maintained at refrigerated conditions. Thus, Solid lipid nanoparticles based novel carrier system has been developed for oral controlled delivery of Cavinton.

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