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Effect of different stabilizer on the formulation of simvastatin nanosuspension prepared by nanoprecipitation technique.

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ABSTRACT

Low oral bioavailability of poorly water-soluble drugs poses a great challenge during drug development. Poor water solubility and slow dissolution rate are issues for the majority of upcoming and existing biologically active compounds. Simvastatin is BCS class-II drugs having low solubility and high permeability. The aim of the present investigation was to find out the effect of different stabilizer on the formulation of simvastatin nanosuspension. Prepared nanosuspensions was evaluated for its particle size study, invitro dissolution study and characterized by Screening Electron microscopy (SEM). The obtained results showed that nanosuspension prepared with the PVPK-30 has improved dissolution rate as compare to all other stabilizer because of decreases in particle size (417nm) as compared to micro suspension of simvastatin. These results indicate the suitability of PVPK-30 as a stabilizer in the formulation of nanosuspension.

Keywords: - Simvastatin, Nanosuspension, Nanoprecipitation, Factorial design

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INTRODUCTION

It is estimated that more than 1/3 of the compounds being developed by the pharmaceutical industry are poorly water soluble. Design and formulation of a different dosage form requires consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients which are to be used in fabricating the product. An important property of a drug substance is solubility, especially aqueous system solubility [1]. The solubility/dissolution behavior of a drug is key factor to its oral bioavailability. The bioavailability of these drugs is limited by their low dissolution rates. To overcome poor solubility, many approaches have been studied. They are generally salt formation, use of surfactant, complexation, solid dispersion, prodrugs and micronization. In micronization the particle size of a drug powder is reduced to a micron scale size (typically 2-10 micron), which increases the specific surface area and dissolution rates. By decreasing the particle size from a micron to a nanometer scale, there is a significant increase in the surface area and related dissolution rate [2, 3].Nanosuspensions are sub-micron colloidal dispersions of pure drug particles in an outer liquid phase. Nanosuspension engineering processes currently used are precipitation [4], high pressure homogenization [5] and pearl milling [6], either in water or in mixtures of water and water-miscible liquids or nonaqueous media [7]. Nano precipitation is a technique where a drug solution in a water miscible organic solvent is mixed with an aqueous solution containing a surfactant(s). Upon mixing, the supersaturated solution leads to nucleation and growth of drug particles, which may be stabilized by surfactants.

Simvastatin (SMS) is a lipid lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, SMS, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG Co-A) reductase, the enzyme that catalyses an early and rate-limiting step in the biosynthesis of cholesterol [12]. SMS is a white, crystalline, non-hygroscopic powder, insoluble in water and 0.1 N HCl (30 μg/ml and 60 μg/ml, respectively). It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption. Improvement of aqueous solubility in such case is a valuable goal to improve therapeutic efficacy. The dissolution rate is a function of the solubility and the surface area of the drug, thus, dissolution rate will increase if the solubility of the drug is increased, and it will also increase with an increase in the surface area of the drug [8, 9].

In this present study, nanoprecipitation technique is used where a drug solution in a water miscible organic solvent is mixed with an aqueous solution containing a surfactant(s). Upon mixing, the supersaturated solution leads to nucleation and growth of drug particles, which may be stabilized by surfactants [10].

The aim of this work is to formulate the SMS nanosuspension by nanoprecipitation method and find out the effect of stabilizer on the formulation, when all parameters of operation are kept constant. The optimize formulation was further characterize by Scanning

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Electron Microscopy (SEM).Dissolution study of nanosuspension formulations was performed in distilled water and was compared to that of micronized suspension of the drug sample[11].

MATERIALS AND METHODS

Materials

Simvastatin and PVPK-30 was obtained as a gift sample from Torrent Pharmaceutical Ltd., Ahmedabad, India. Acetone, Acetonitrile, Sodium lauryl sulphate (SLS), Tween-80,Poly Vinyl alcohol (PVA) was obtained as a gift sample from S.D.Fine Chemicals Ltd., Mumbai, India. Bidistilled water was prepared in laboratory for study. All materials used for study conformed to USP-24 standards.

Preparation of simvastatin nanosuspensions by nanoprecipitation technique

Nanosuspensions were prepared by the nanoprecipitation technique. Simvastatin was dissolved in an acetone at room temperature. This was poured into fixed amount of water containing fixed amount of different stabilizers at a room temperature and subsequently stirred on magnetic stirrer to allow the volatile solvent to evaporate (Remi, magnetic stirrer, India.). Addition of organic solvents by means of a syringe positioned with the needle directly into stabilizer containing water. Organic solvents were left to evaporate off under a slow magnetic stirring of the nanosuspension at room temperature for 1 hour. (Table1)

Particle size determination

Particle size was determined by photon correlation spectroscopy (PCS) using a Zetasizer 3000 (Malvern Instruments, UK). This analysis yields the mean diameter (z-average, measuring range: 20–1000 nm). All the data presented are the mean values of three independent samples produced under identical production conditions.

Screening electron microscopy

Particle size and morphology were examined by SEM, The particle size distribution was determined by the IBAS I/II Image Analyzer System (Germany) via the obtained SEM photographs.

Dissolution study

In-vitro drug release studies were performed in USP apparatus-Type II using paddle method at rotation speed of 50 rpm. Dissolution was carried out in distilled water as a dissolution medium. The volume and temperature of the dissolution medium were 900ml and 37.0 ± 0.5^{o}c. 5 ml of sample was withdrawn periodically (after 5 minutes) and replaced with an equal volume of fresh distilled water up to 60min. Samples were suitably diluted and filtered

through a filter paper (0.22 µm, Whatman Inc., USA). The filtrate was then subject to the UV analysis against the blank (distilled water). Percent cumulative release of SMS was calculated based on the standard UV calibration curve at 233nm (Systronic 2203, Japan).

RESULT AND DISCUSSION

Nanoprecipitation has been employed to produce nanosuspension of simvastatin. The types of different stabilizer were contributing much towards the change in particle size in nanosuspension preparation. Nanosuspension of simvastatin was prepared by as formulation shown in table 1. P_1–P_6 formulations were containing different concentration of different stabilizer. Amount of water and acetone was kept constant for all batches. Bluish white transparent nanosuspension was successfully prepared which was compared with distilled water (figure 1).

Influence of stabilizers on particle size

The stabilizer's characteristics play an important role in creating a stable formulation. It must be capable of wetting the surface of the drug crystals and providing a steric or ionic barrier. Too little stabilizer induces aggregation or agglomeration and too much stabilizer promotes Oswald's ripening. First of all a screening of formulations was designed with different polymeric, anionic and stearic stabilizers. PVA, PVPK30, is a well known efficient polymeric stabilizer forming adsorption layers on drug nanoparticles and SLS was efficient anionic stabilizer, Poloxamer-407 & Poloxamer 188 it can form a substantial mechanical and thermodynamic barrier at the interface that retards the approach and coalescence of individual emulsion droplets at their optimum level.

It was observed that the particle size (nm) and rate of dissolution has been improved when nanosuspension prepared with the PVPK-30 because of the efficient adsorption of the stabilizer on the produced nanoparticles surface and also imparts the stability to the formulation. The rate of dissolution of the optimized nanosuspension (P_2) was enhanced (50% in 14 min), relative to micronized suspension of simvastatin (50 % in >>6hr), mainly due to the formation of nanosized particles.

Particle size

The particle size of different formulation was shown in figure 2, which clearly indicates the batch P_2 had less particle size as compare to other formulation. The batch (P_2) had a Z-average particle size of 417 nm with 0.225 poly dispersivity index which indicate the particles are in uniform distribution. The particle size distribution pattern of the nanosuspension prepared with PVPK-30 formulation is given in figure 3.

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In-vitro dissolution studies from nanosuspension

Fig. 4 shows the dissolution behavior of simvastatin and its nanosuspensions. The release rate profiles were drawn as the percentage simvastatin dissolved from the nanosuspension and pure drug versus time. Dissolution studies of pure simvastatin and all other prepared nanosuspension (P1- P6) were carried out in distilled water. t50% (time to dissolve 50% drug) values calculated from release profile are reported in Table 2. From this data, it was evident that onset of dissolution of pure simvastatin was very low as compare to its nanosuspension.

Scanning electron microscope analysis of batch P2

The nanoparticles surface appearance and shape were analyzed by scanning electron microscopies (SEM) figure 5. This was indicating the size and shape of the prepared nanosuspension.

Ingredients	P1	P2	P3	P4	P5	P6
Simvastatin(mg)	10	10	10	10	10	10
PVA(mg)	30					
PVPK-30 (mg)		30				
SLS (mg)			4			
Tween-80(ml)				2		
Poloxamer-407(mg)					30	
Poloxamer-188(mg)						30
Acetone(ml)	1	1	1	1	1	1
Water(ml)	40	40	40	40	40	40

Table 1.Formulation of Simvastatin nanosuspension using different stabilizer

Batch code	P1	P2	P3	P4	P5	P6	Pure drug
t 50%	19	14	18	24	20	24	>>6 hr

Table-2 Time to dissolve 50% drug (t50%) from pure simvastatin and its nanosuspensions

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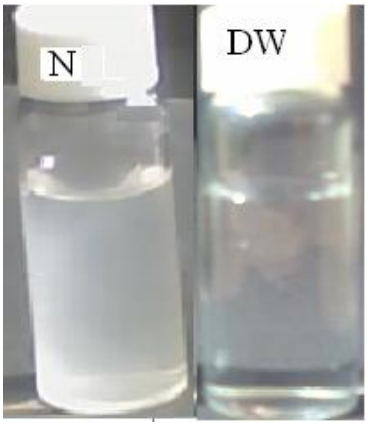

Figure:- 1

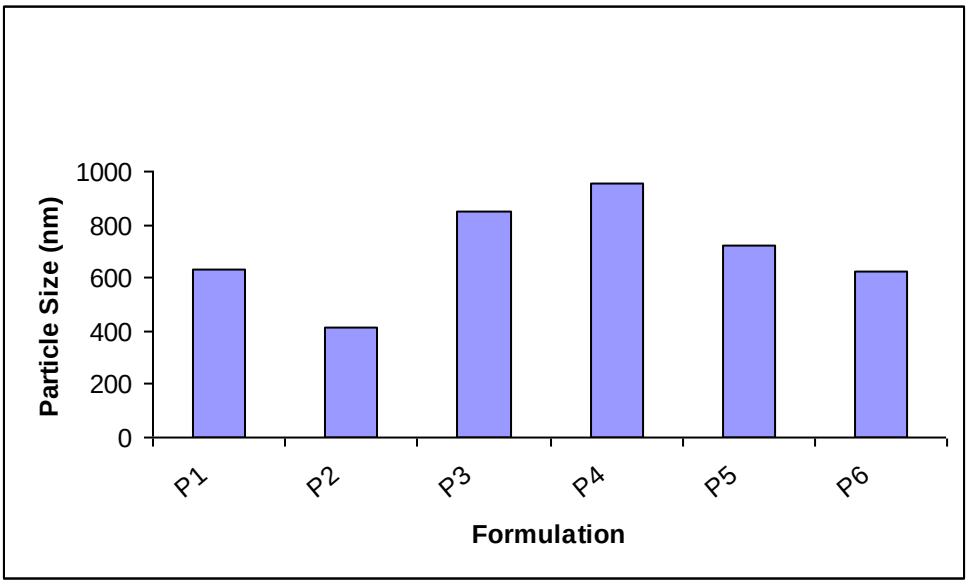

Figure: - 2Comparision of particle size with different stabilizer.

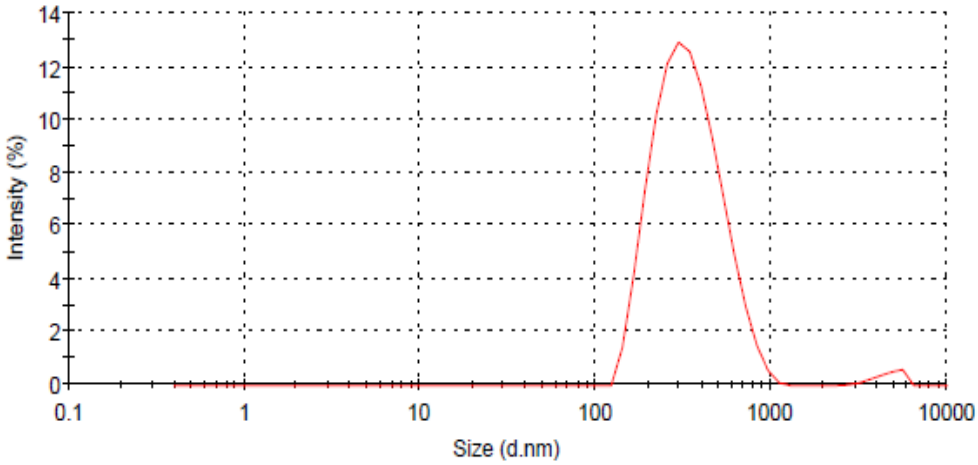

Figure: - 3 Particle size graph of batch P_2

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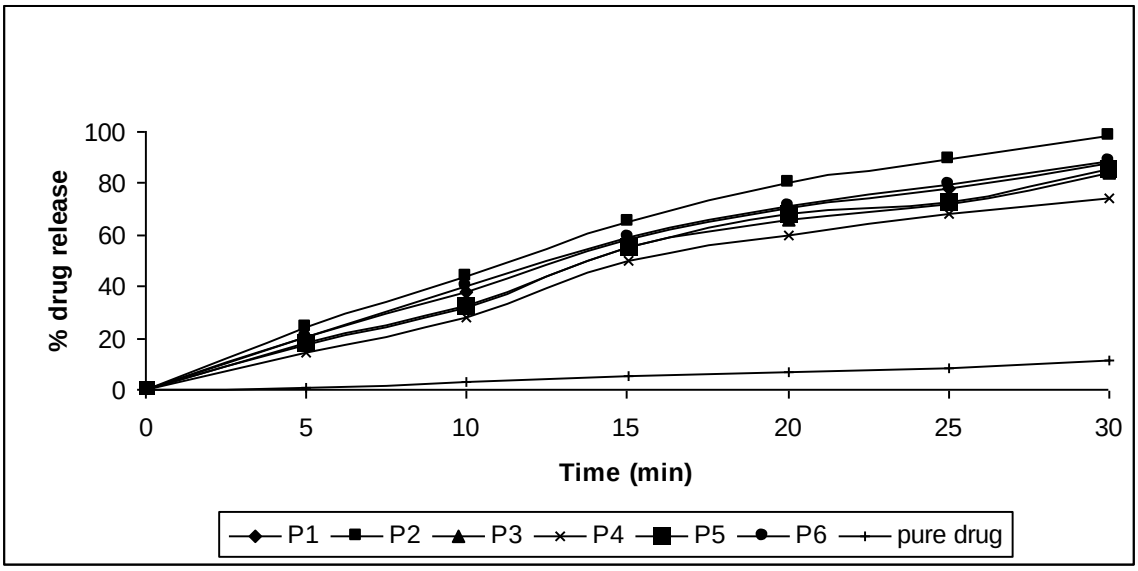

Figure: - 4 Comparision of dissolution profile of batch P_1 to P_6 with pure drug

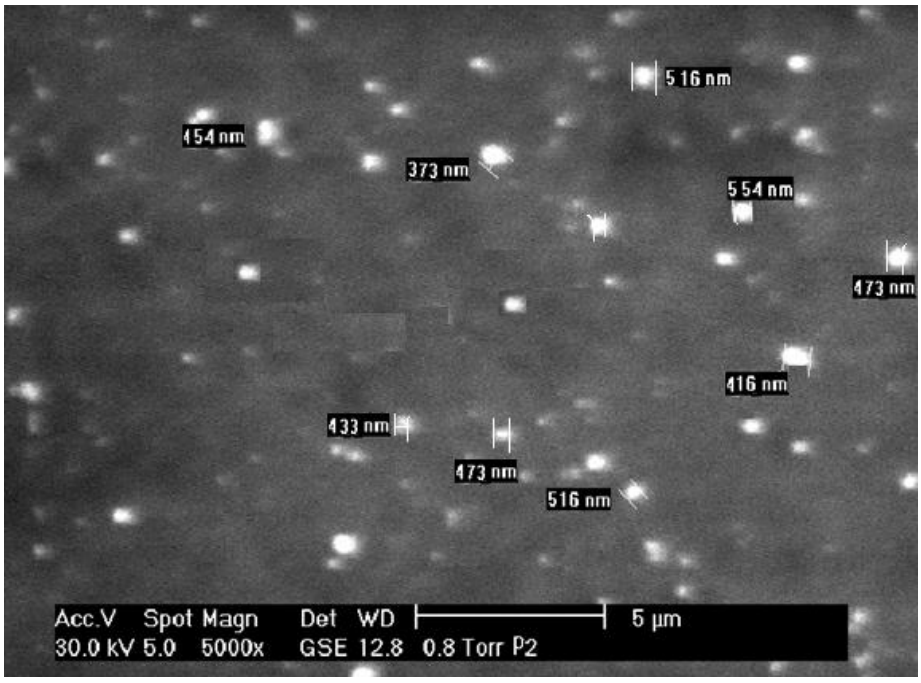

Figure: - 5 SEM of batch P_2

CONCLUSION

A nanoprecipitation method was developed to prepare simvastatin nanoparticles using PVPK-30 as stabilizer. In this process, the particle size of simvastatin can be obtained in the micron and nano-size ranges by selecting proper stabilizer. The best nanosuspension of

simvastatin can be obtained by PVPK-30 as a stabilizer using nanoprecipitation technique. The dissolution of nanosized simvastatin is significantly enhanced compare with the pure simvastatin suspension. In conclusion, the nanoprecipitation method offers a direct process to obtain drug nanoparticles of desirable size, amenable for continuous and consistent production.

ACKNOLEDGEMENT

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