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Original Article

Develop oral suspension of dasatinib by solvent evaporation method using various stabilizers and surfactants such as poloxamer, tween 80 and PVA

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ABSTRACT

The present investigation aimed at enhancing the oral bioavailability of Dasatinib by improving its solubility and dissolution rate by preparing nanosuspensions. The nanosuspensions of Dasatinib were prepared using emulsification solvent evaporation method by Poloxamer, PVA & Tween 80. Various formulation as well as process parameters were optimized in order to achieve desirable size and saturation solubility. Characterization of the prepared nanosuspension was done with respect to particle size, zeta potential, saturation solubility, dissolution rate, morphology study (SEM), in-vitro dissolution study. From invitro drug release studies, F9 formulation containing PVA & tween 80 (0.2mL) is considered as optimized formulation as it shows drug release with in 45minutes, while all the remaining formulations shows drug release at 60min and follows first order kinetics. Nanosuspension seems to be a promising approach for bioavailability enhancement because of the simple method of its preparation and its universal applicability.

Keywords: Dasatinib, Poloxamer, PVA, Tween 80.

INTRODUCTION

Many of the modern chemical entities produced by drug discovery programmers (approximately 40% or more) are poorly water soluble. Pharmaceutical scientists have long faced a tough issue with the formulation of low water soluble drugs. Bioavailability is weak due to the low saturation solubility and dissolution speed. For BCS class II drugs such as iron-conazole and carbamazepine, the issue is more serious because they are poorly overcome both in aqueous and organic medium. Dissolution-rate-limited efficiency of these medications is impaired by the patient's feed / fast condition. Both the shape and size of the particles are correlated with dissolution rates of sparingly soluble products. Therefore the breakdown rate is improved due to a reduction in particle size. There are several formulation methods to address the problems associated with low solubility of Class II drugs and low bioavailability. Micronization, solubility using cosolvents, use of permeation enhancers, dispersion of surfactants, salt forming and precipitation strategies are some of the

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solutions for increasing solubility. Most of these strategies have benefits and some disadvantages for maximising solubility and thus have limited usefulness in improving solubility. Other solutions used to improve solubility, such as microsphere, emulsion, micro emulsion, liposome processing and supercritic processing, solid dispersion and cyclodextrin inclusion complexes, demonstrate good success, but are not universal with all drugs that are not soluble both aqueous and organic. Because of its versatility and its superiority over other methods, nanosuspensions have shown their capacities to take on the problems involved with the supply of poorly water-soluble and lipid soluble drugs.[1-3]

The concept of a Pharmaceutical Nanosuspension is strongly colloid, biphasic and scattered solid drug particles in an aqueous car, with a surfactant and polymer scale of less than 1μm and stabilisation, prepared with adequate drug delivery methods. The ability of Nanosuspension to solve the issue of the supply of water-poorly soluble and lipid-soluble medicine has been shown. It increases the absorption and bioavailability of traditional oral doses and helps reduce the dosage.[4]

MATERIALS AND METHODS

Dasatinib was procured from B.M.R.Chemicals, Hyderabad. Tween 80, PVP K30, Poylvinyl chloride, was procured from Rankem, Mumbai. All other chemicals used were of analytical grade.

Solubility studies: Solubility of Dasatinib was determined in Methanol, Ethanol, pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Dasatinib in different beakers containing different solvents. The mixtures were shaken for 48 hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 318 nm by using UV Spectrophotometry.[4]

Method of Preparation of Nanosuspension:-

Preparation of Dasatinib Nanosuspension by Emulsification solvent evaporation method: Nanosuspension was prepared by the Emulsification solvent evaporation technique. Dasatinib was dissolved in methanol at room temperature (organic phase). This solution is followed by its emulsification into water containing different stabilizers of Poloxamer, PVA, and TWEEN 80 maintained at room temperature. Addition of organic solvents by means of a syringe positioned with the needle directly into stabilizer containing water, and subsequently stirred on magnetic stirrer to allow the volatile solvent to evaporate. Evaporation leads to precipitation of the drug. [5-7] Formulation was tabulated in table 1,2.

Evaluation parameters of Nanosuspension Dasatinib:[5-11]

Entrapment efficacy: The freshly prepared nanosuspension was centrifuged at 20,000 rpm for 20 min at 5°C temperature using cool ultracentrifuge. The amount of un-incorporated drug was measured by taking the absorbance of the appropriately diluted 5 ml of supernatant solution at 318 nm using UV spectrophotometer against blank/control nanosuspensions. DEE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken.

The entrapment efficiency (EE %) could be achieved by the following equation:

%Entrapment efficiency= Drug content *100/Drug added in each formulation

Scanning electron microscopy: The morphological features of Dasatinib nanosuspension are observed by scanning electron microscopy at different magnifications.

Zeta potential: There are three ways by which a solid particle (colloid) dispersed in a liquid media can acquire a surface charge. First, by the adsorption of ions present in the solution. Second, by the ionization of functional groups on the particle's surface. Third, due to the difference in dielectric constant between the particle and the medium. Attention should be paid to the formation of electric double layer at the solid-liquid interface. The zeta Potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. The potential gradually decreases as the distance from the surface increases.

As the concentration of electrolyte increases in the medium, the zeta potential falls off rapidly due to the screening effect of the counter ions. The zeta potential cannot be measured directly; however, it can be calculated using theoretical models and from experimentally determined electrophoretic mobility data. The theory is based on electrophoresis and can be expressed as:-

$$\mu = \zeta\varepsilon/\eta$$

Where (μ) is the electrophoretic mobility, (ε) is the electric permittivity of the liquid, (η)
Is the viscosity and (ζ) us the zeta potential.

***In vitro* drug release study:** In vitro dissolution study was performed by USP dissolution apparatus-type II using 900 ml of 6.8pH buffer as a dissolution medium maintained at 37 ± 0.5°C and stirring speed (50 rpm). The freshly prepared nanosuspensions were added to the dissolution medium, five-milliliter samples were withdrawn at

specific intervals of time, then filtered through a 0.45 µm filter paper and analyzed for their drug concentrations by measuring at 318 nm wavelength.

The results of in vitro release profiles obtained for the NDDS formulations were fitted into
Two models of data treatment as follows:
1. Cumulative percent drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining versus time (first- order kinetic model).

RESULTS AND DISCUSSION

Solubility studies: From the above conducted solubility studies in various buffers we can say that 0.1N HCl phosphate buffer has more solubility when compared to other buffer solutions. So 0.1N HCl buffer is used as dissolution medium, based upon the solubility studies on organic solvents methanol has more solubility than others so methanol was used in the nanosuspension formulation.

Entrapment efficacy: The entrapment efficacy of formulation F1 was found to be 95.24%, formulation F2 was found to be 96.35%, formulation F3 was found to be 98.12%, formulation F4 was found to be 95.78%, formulation F5 was found to be 96.32%, formulation F6 was found to be 98.12 %, formulation F7 was found to be 96.42 %, formulation F8 was found to be 96.35%, formulation F9 was found to be 95.87%., formulation F10 was found to be 98.12 %, formulation F11 was found to be 95.36 %, formulation F12 was found to be 96.87%.

Invitro drug release studies: Total 12 formulations was developed using Poloxamer, PVA & Tween 80. By using PVA & tween 80, formulation F1-F3 was formulated in which F1 formulation shows maximum drug release of 86.37% at 60min. While F2 formulation shows 90.38% of drug release at 60min. Where F3 formulation shows 94.28% drug release at 60min.
F4-F6 formulations were formulated using Poloxamer & tween 80, in which F4 formulation shows maximum drug release of 79.35% at 60min. While F5 formulation shows 83.75% drug release at 60min. Where F6 formulation shows 89.45% of drug release. Further trials was formulated by varying the ratio of tween 80. F7-F8 formulations was formulated using PVA & tween 80 (0.2mL), in which F7 formulation shows maximum drug release of 92.46% at 60min. While F8 formulation shows 99.45% of drug release at 60min. Where F9 formulation shows 98.75% drug release at 45min. So by increasing the ratio of tween 80 reveals that drug release time was decreased.

F10-F12 formulation was formulated using Poloxamer & tween 80 (0.2mL). in which F10 formulation shows maximum drug release of 87.16% at 60min. While F11 formulation shows 95.28% of drug release at 60min. Where F12 formulation shows 95.72% drug release at 45min.
Among all the formulations, F9 formulation is considered as optimized formulation as it shows drug release with in 45minutes. Results were tabulated in figure 1.

Drug release kinetics studies: The drug release from the Nanosuspension was explained by using mathematical model equations such as zero order, first order, and equation methods. Based on the regression values it was concluded that the optimized formulation F9 follows first order kinetics, indicating concentration dependent drug release.

CONCLUSION

In present investigation Nanosuspensions of Dasatinib was prepared by Emulsification solvent evaporation method. The Nano suspensions are novel promising target and controlled released dosage form which is gaining importance because of ease of manufacturing and diversified applications. The present trend of pharmaceutical research lies in the usage of biodegradable polymer because of its availability and low toxicity. Nanosuspension containing drug was prepared by emulsification solvent evaporation method by using combinations of Tween 80, Poloxamer, PVA, methanol and quantity sufficient water). Zeta potential value for the optimized formulation (F9) was found within the range which was found to be within the acceptable limits. Average particle size of nanosuspension of optimized formulations (F9) was found to be within the range. From the invitro studies we can say that formulation F9 shows best drug release of 98.53% within 45 minutes when compared to all the remaining formulations. The drug release from the Nanosuspension was explained by the using mathematical model equations such as zero order, first order, and equation methods. Based on the regression values it was concluded that the optimized formulation F9 follows first order kinetics.

Table 1: Formulation Table of Dasatinib Nanosuspension (F1-F6)

Ingredients	Formulation code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Dasatinib (mg)	160	160	160	160	160	160
PVA (mg)	50	75	100	--	--	--
Poloxamer (mg)	--	--	--	50	75	100
Tween 80 (ml)	0.1	0.1	0.1	0.1	0.1	0.1
Methanol (ml)	5	5	5	5	5	5
Water (ml)	40	40	40	40	40	40

Table 2: Formulation Table of Dasatinib Nanosuspension (F7-F12)

Ingredients	Formulation code					
	F7	**F8**	**F9**	**F10**	**F11**	**F12**
Dasatinib (mg)	160	160	160	160	160	160
PVA (mg)	50	75	100	--	--	--
Poloxamer (mg)	--	--	--	50	75	100
Tween 80 (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Methanol (ml)	5	5	5	5	5	5
Water (ml)	40	40	40	40	40	40

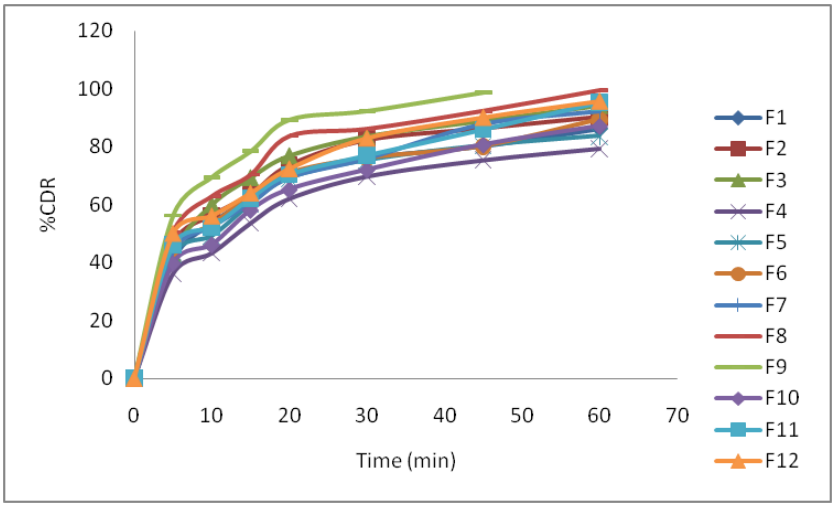

Fig. 1: % CDR of Dasatinib Nanosuspensions (F1 – F12)

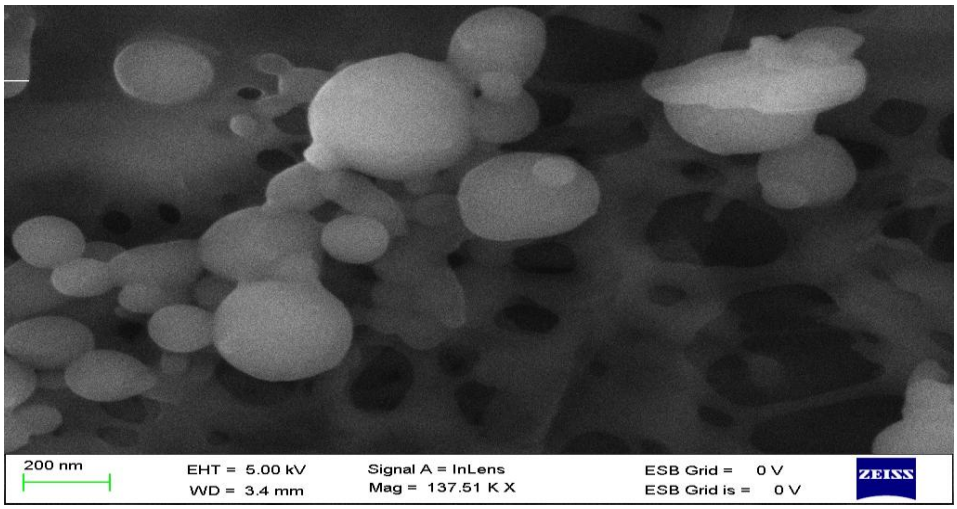

Fig. 2 : Scanning Electron Microscopy of Optimized Formulation (F9)

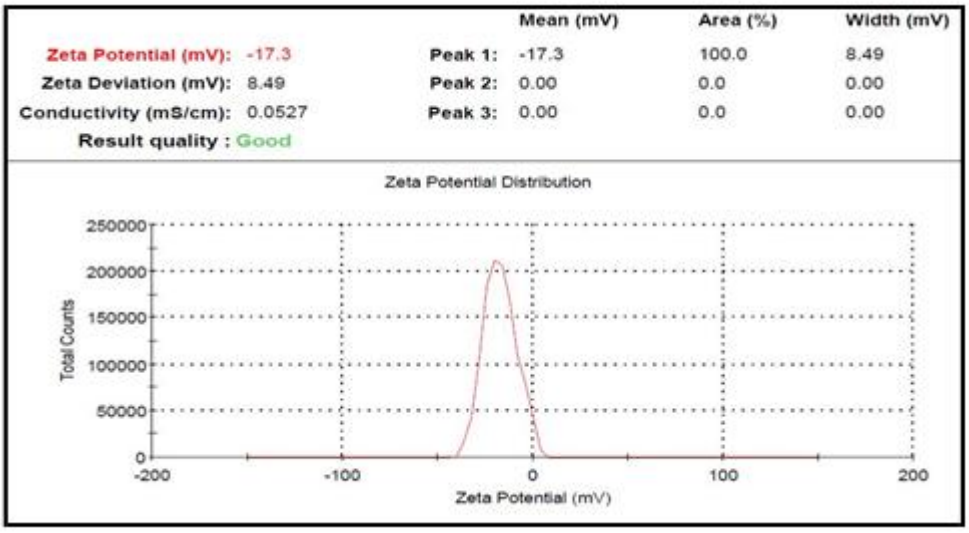

Fig. 3: Zeta potential value for the optimized formulation (F9)

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