Journal of Advanced Pharmacy Education & Research
2: 189-194 (2011) ISSN 2249-3379

Enhancement of dissolution of poorly water soluble raloxifene hydrochloride by preparing nanoparticles

Ashok Kumar Suthar*[1], Shailendra Singh Solanki[2], Rakesh Kumar Dhanwani[3]

1. Sandoz Pvt. Ltd., Belapur Road, Thane, Navi Mumbai, India.
2. Department of Pharmaceutics, College of Pharmacy, IPS Academy, Rajendra Nagar, Indore, India.
3. Formulation Research and Development, Dr. Reddy's Laboratories Ltd., Hyderabad. India.

*Corresponding author: sss.solanki@gmail.com

ABSTRACT:

Nanoparticle engineering offers promising methods for the formulation of poorly water soluble drug compounds. The aim of the present work was to enhance dissolution and oral bioavailability of poorly water-soluble Raloxifene Hydrochloride (RH) by preparing stable nanoparticles. Mechanism of dissolution enhancement was also investigated. nanoparticles were produced by combining the antisolvent precipitation and high pressure homogenization (HPH) approaches in the presence of HPMC E5 and SDS (2:1, w/w). Then the nanosuspensions were converted into dry powders by spray-drying. The effect of process variables on particle size and physical state of drug were investigated. The physicochemical properties of raw RH and nanoparticles were characterized by Scanning Electron Microscopy (SEM). The images of SEM revealed spherical RH nanoparticles. Nanoparticles showed good dissolution profile. The process by combining the antisolvent precipitation under sonication and HPH was produce small, uniform and stable nanoparticles which markedly enhanced dissolution rate.

Key words: Nanoparticles, Raloxifene Hydrochloride, Dissolution, Antisolvent.

INTRODUCTION:

The poor solubility and slow dissolution rate of many drugs are a major industrial problem, especially for pharmaceutical scientists involved in drug discovery and drug development. It has been reported that about 40% of the compounds being developed by the pharmaceutical industry are poorly water soluble or "insoluble" in water [1-2]. Poor water solubility is the major hurdle to be overcome in the case of poorly water

soluble drugs in terms of their vivo performance due to their inadequate ability to be wetted by and dissolved in the fluid. Hence, improving the solubility and dissolution rate of poorly water soluble drugs is very important and significantly challenging to pharmaceutical researchers seeking to achieve optimum absorption of new drug candidates. According to the Noyes-Whitney equation, the saturation solubility and dissolution rate of poorly water soluble drugs can be enhanced by reducing the particle size to the nano- range, thus increasing the interfacial surface area [3-4].

In recent years, nanoparticle engineering processes have become promising approaches for the enhancement of dissolution rates of poorly aqueous soluble drugs [5-7]. The formation of nanoparticles is based on cavitation forces, collisions as well as shear forces created in high pressure homogenizers such as the piston-gap homogenizer [8].

Raloxifene hydrochloride (RH) is a selective estrogen receptor modulator (SERM) shown to be effective in the prevention of osteoporosis with potential utility as a substitute for long-term female hormone replacement therapy [9]. RH is a poorly water soluble drug known to demonstrate dissolution and solubility limited absorption [10]. Although the RH being a low solubility drug with high permeability, is classified a Class II drug in BCS adopted by USFDA. Hence, increasing the solubility of RH may enhance its dissolution. Thus the aim of this study was to prepare and investigate the properties and mechanism of dissolution enhancement of RH- nanoparticles.

MATERIALS AND METHODS:

Materials

Raloxifene HCl was purchased from Jubilant Organosys Manufactured by Glochem Laboratory, Hyderabad, India. Hydroxypropyl Methylcellulose (HPMC E5) was obtained from Signet Chemicals. Sodium Dodecyl Sulfate (SDS) and Tween 80 were obtained from Tianjin Bodi Chemical. Methanol and Ethyl Acetate was of chromatographic grade and all other chemicals, reagents and solutions used were of analytical grade.

Preparation of nanosuspensions:

Nanosuspensions were prepared in the following two steps. Firstly, the initial RH suspensions were produced by antisolvent precipitation under sonication. Acetone and water were used as solvent and antisolvent respectively and the ratio of solvent to antisolvent was 1:20. Raw RH was completely dissolved in 10 mL acetone to prepare an organic solution of RH, and this solution was then injected into 200 mL 0.15% (w/v)

aqueous solution (containing HPMC E5 and SDS, 2:1, w/w) under sonication for 5 min. Continuous sonication was applied via a probe sonicator. Thus, preliminary RH suspensions were obtained and labeled as SO-RH. The suspensions were kept under vacuum at room temperature for 2 h to remove the acetone. Then, the RH suspensions were further homogenized by high pressure homogenization, using a homogenizer at 500 bars for 8 minutes to obtain the final product, RH nanosuspensions labeled as SHSO-RH.

Spray-drying of RH nanosuspensions

Spray-drying was used for solidification of RH nanosuspensions. A spray dryer was used to convert RH nanosuspensions into dry powders. The aspirator was operated at 0.6 m^3/min and the pump was set at 5 mL/min. The dry powder with nanosized RH exhibited good uniformity and the yield of dry powder was approximately 82%.

Characterization of RH nanoparticles

Scanning Electron Microscopy:

The morphologies of raw RH and nano-sized RH were examined using a Scanning Electron Microscope (JEOL JSM-7001F, Japan) operated at an accelerating voltage of 15 kV and a secondary detector.

***In vitro* dissolution studies:**

Drug release studies were performed on plain drug (60 mg), physical mixture and spray-dried powder with nano-sized drug; RH (6 tablets in triplicate) on dissolution test apparatus (Electrolab India Ltd) at 37 + 0.5 °C employing USP apparatus II at 50 rpm. Water, Phosphate buffer (pH 6.8, 0.5% SDS) was employed as the dissolution medium. Dissolution studies were performed on pure drug (60 mg) and spray-dried powder with nano-sized drug (RH) containing equivalent amount of the drug. Aliquots of the periodically withdrawn samples (10 ml) were analyzed spectrophotometrically at 287.0 nm and were replaced with an equal volume of plain dissolution medium.

RESULTS AND DISCUSSION:

Preparation of nanoparticles of Raloxifene Hydrochloride (RH):

In this work, Raloxifene Hydrochloride (RH) nanoparticles were successfully prepared by the combination of antisolvent precipitation and HPH. When a combination of HPMC E5 and SDS (2:1 w/w) was selected as the stabilizer, smaller submicron particles were

obtained. When the stabilizer concentration was below 0.1%, the mean particle size was about 800 nm and can be increased easily. As the stabilizer concentration increased to 0.15%, the mean particle size was dramatically reduced to 159 nm and particle growth can be controlled well by stabilizers. Following a further increase in stabilizer concentration, the particle size was not markedly reduced, which indicated that the drug particle surface was already sufficiently enveloped by the stabilizer molecules.

The morphology of RH nanoparticles

The SEM images are showed in Figure 1. RH nanoparticles obtained by the combination of antisolvent precipitation and HPH were spherical in the presence of a combination of HPMC and SDS (2:1, w/w) (Fig. 1). Moreover, the nano-sized particles were very thin revealed by the presence of fragments. It was clearly seen that stabilizers were adsorbed onto the drug particle surface inhibiting particle growth. The images also revealed that these agglomerates or particle assemblies were composed of a large number of individual nanoparticles.

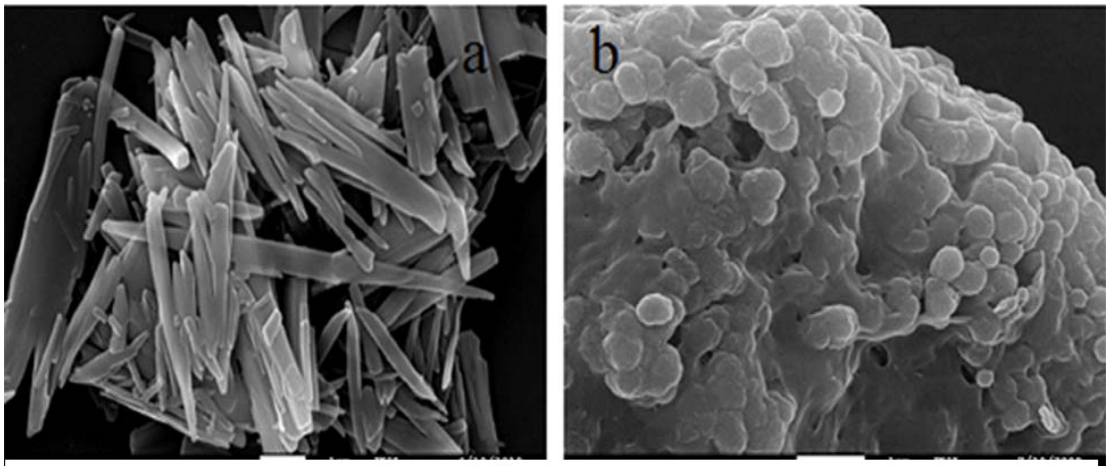

Figure 1: SEM images of raw RH (a) and RH-nanoparticles (b)

***In vitro* dissolution study:**

Table 1 showed the saturation solubility of raw RH and SHSO-RH. The results of the solubility study indicated that pure RH possesses a very low solubility in water. The saturation solubility of SHSO-RH was approximately four times that of raw RH. The profiles shown in Figure 2 illustrated the dissolution rates of raw RH and SHSO-RH. Nano-sized RH displayed a dramatic increase in the rate and extent of dissolution in comparison with raw drug, especially SHSO-RH exhibited 79% drug dissolution within 20min whereas only 19% of raw RH dissolved during the same period. After 30 min, SHSO-RH was dissolved 97%, but only 33% of raw RH had dissolved, owing to its

crystalline nature and larger crystal size. The dissolution profiles of PM was similar to that of raw drug, which showed that the mechanical physical mixing of raw RH and stabilizers had little effect on the dissolution of raw Raloxifene Hydrochloride (RH).

Table 1. The saturated solubility: raw drug (RH); Physical-Mixture (PM) and SHSO-RH

S. No.	Sample	Saturated solubility (%)
1.	RH	7.57
2.	Physical Mixture (PM)	8.12
3.	SHSO-RH	30.67

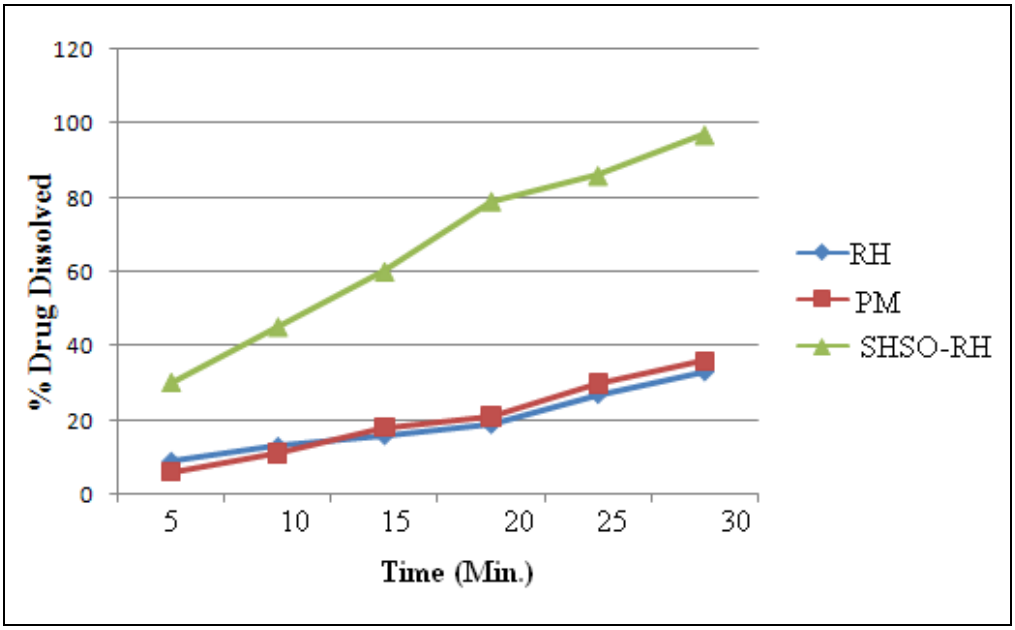

Figure 2. The dissolution profiles: raw drug (RH); Physical-Mixture (PM) and SHSO-RH

CONCLUSION:

The stable amorphous RH nanoparticles were successfully prepared by antisolvent precipitation under sonication followed by high pressure homogenization (HPH) and the nanosuspensions were converted into dry powders by spray-drying. The amorphous RH in nanoparticles formed in the procedure of antisolvent precipitation under sonication

and kept the state during HPH and spray-drying. The amorphous RH nanoparticles exhibited different surface property and improved wettability compared with the pure drug due to different molecular structural arrangements. The nanoparticles showed dramatic improvement in rate as well as extent of *in-vitro* drug dissolution. The improvement can be attributed to amorphization, better wettability, increased saturation solubility and surface area, reduced particle size and decreased diffusion layer thickness. Results of work suggested that nanonisation can be a good technique for the formulation of poorly water soluble drugs.

REFERENCES:

1. Radtke M. Pure drug nanaoparticles for the formulation of pooly soluble drugs. New Drugs. 2001; 3: 62-68.
2. Lipinski C. Poor aqueous solubility-an industry wide problem in drug discovery. Am. Pharm. Rev. 2002; 5: 82-85.
3. Dressmann J.B., Reppas C. In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs. Eur. J. Pharm. Sci. 2000; 11: 73-80.
4. Kesisoglou F., Panmai S., Wu Y. Nanosizing-oral formulation development and biopharmaceutical evaluation. Adv. Drug. Deliv. Rev. 2007; 5916: 31-44.
5. Patravale V.B., Date A.A., Kulkarni R.M. Nanosuspensions: a promising drug delivery strategy. J. Pharm. Pharmacol. 2004; 56: 827-840.
6. Rabinow B.E. Nanosuspensions in drug delivery. Nature rev. Drug Disc. 2004; 3: 785-796.
7. Wong S.M., Kellaway I.W., Murdan S. Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles. Int. J. Pharm. 2006; 317: 61-68.
8. Muller R.H., Jacobs C., Kayser O. Nanosuspension as particulate drug formulations in therapy rationale for development and what we can expect for the future. Adv. Drug Deliv. Rev. 2001; 47: 3-19.
9. Mitlak B.H., Cohen F.J. In search of optimal long-term female hormone replacement: the potential of selective estrogen receptor modulators. Horm. Res. 1997; 48:155-163.
10. Wempe M.F., Wacher V.J., Ruble K.M., Ramsey M.G., Edgar K.J., BuchananN.L., Buchanan C.M. Pharmacokinetics of raloxifene in male Wistar–Hannover rats: Influence of complexation with hydroxybutenyl-beta-cyclodextrin, Int. J. Pharm. 2008; 346:25-37.