ABSTRACT

Drug absorption from the gastro intestinal tract can be limited by various factors with the most common one being poor aqueous solubility and poor permeability of a drug molecule. When delivering an active ingredient orally, it must first dissolve in gastrointestinal fluids before it permeate the membranes of the gastro intestinal tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will exhibit dissolution rate limited absorption. Solubility behaviour of a drug plays a key role for its oral bioavailability. For some drugs solubility presents a challenge to the development of a suitable formulation for oral administration. Therefore solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs.

Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach was fast dissolving tablets which have gained acceptance and popularity in the recent time. Several pharmaceutical industries prepared fast dissolving tablets by direct compression technique by selecting suitable super disintegrants. Direct compression technique offers important advantages such as increased output, reduced cost, less machinery and improved drug stability when compared to the wet granulation method.
The aim of the work was to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble drugs Atorvastatin Calcium and Rosuvastatin Calcium by formulating them as solid dispersions using various techniques with PEG-6000 as a carrier and subsequent preparation of fast dissolving tablets with the prepared solid dispersions using different concentrations of super disintegrants and comparing them with that of the marketed product.

Atorvastatin Calcium is a HMG-CoA reductase inhibitor used in the treatment of dyslipidemia and prevention of cardiovascular disease. It is very slightly soluble in water, slightly soluble in ethanol and freely soluble in methanol. Atorvastatin Calcium is rapidly absorbed after oral administration with absolute bioavailability of parent drug is approximately 12% and is hydrolysed in the liver to ortho and para hydroxylated derivatives. Peak plasma concentrations achieved with in 1-2 hours. The half life is 14 hours.

Rosuvastatin Calcium is a lipid regulating drug, it is a competitive inhibitor of HMG-CoA used to reduce cholesterol, used in the treatment of osteoporosis, benign prostatic hyperplasia, dysbetalipoproteinemia and alzheimer's disease. It is sparingly soluble in water, ethanol and soluble in methanol. Rosuvastatin Calcium is absorbed from the gastrointestinal tract and is metabolised in the liver. Peak plasma concentrations achieved with in 3-5 hours. The half life is 19 hours.

Based on their physicochemical and biopharmaceutical properties, Atorvastatin Calcium and Rosuvastatin Calcium were selected as drug
candidates for developing solid dispersions formulations for improving its solubility and bioavailability by improving the dissolution rate.

In the present investigation Atorvastatin Calcium and Rosuvastatin Calcium solid dispersions were prepared by physical mixing, fusion, solvent evaporation and lyophilisation methods using polyethylene glycol-6000 as an inert carrier. The prepared solid dispersions were evaluated for precompressional parameters such as angle of repose, carr’s index, particle size and drug content further in vitro dissolution studies were performed on all the prepared solid dispersions by using USP type II dissolution apparatus with 900ml pH 6.8 phosphate buffer maintained at 37±0.5°C with a paddle speed of 50 rpm. The dissolution parameters such as \(T_{50}\), \(T_{90}\), \(DE_{20}\%), K, R^2 were calculated for all the solid dispersions. The pure drug Atorvastatin Calcium and Rosuvastatin Calcium along with optimized solid dispersions were characterized by DSC, PXRD, IR and SEM analysis.

The Atorvastatin Calcium and Rosuvastatin Calcium optimized solid dispersions which shows better dissolution rate were then formulated as fast dissolving tablets by using newer super disintegrants such as pregelatinised starch, sodium starch glycolate, croscarmellose sodium, crospovidone. All the tablet formulations were evaluated for physical parameters such as weight uniformity, hardness, friability, wetting time, dispersion time and drug content were evaluated as per the IP specifications. All the batches of tablet formulations were subjected to in vitro dissolution studies as per the earlier stated method for solid dispersions. All the dissolution parameters such as \(T_{50}\), \(T_{90}\), \(DE_{20}\%), K, R^2 were calculated for all the tablet formulations. Based on the in vitro dissolution studies optimized fast dissolving tablets of
Atorvastatin Calcium and Rosuvastatin Calcium were further subjected to in vivo pharmacokinetic studies.

*In vivo* pharmacokinetic studies for the optimized fast dissolving tablets of Atorvastatin calcium and Rosuvastatin calcium were carried out in albino rabbits. The tablet formulations were dispersed in distilled water and fed to different group rabbits through oral route by using soft oral tube. The blood samples were withdrawn from the rabbits at various time intervals and plasma was separated. The plasma drug concentrations were estimated by using HPLC method. The amount of drug available in plasma versus time plots were drawn and the pharmacokinetic parameters such as $C_{\text{max}}$, $T_{\text{max}}$, $T_{\frac{1}{2}}$, AUC (0-t), AUMC (0-t), MRT were calculated by using PK summit solutions software USA.

The fast dissolving tablets of Atorvastatin Calcium and Rosuvastatin Calcium subjected to in vivo pharmacokinetic studies were also tested for stability by accelerated stability studies. These tablets were stored at 25±2°C, 60±5% RH for 6 months and 40±2°C, 75±5% RH for 3 months. Then samples of tablet formulation were further evaluated for physical parameters and the tablets were subjected to in vitro dissolution studies.

The results of the present investigation clearly indicated that the preparation of solid dispersions by physical mixing, fusion, solvent evaporation and lyophilisation methods greatly improved the solubility and dissolution rate of poorly soluble drugs, Atorvastatin Calcium and Rosuvastatin Calcium. PEG-6000 used as an inert carrier was found suitable for the preparation of solid dispersions by various methods. It was observed that as the proportion of PEG-6000 concentration increased the
solubility and dissolution characteristics were improved for the solid dispersions. All the solid dispersions exhibited good flow characteristics with uniform particle size. Among the various method of preparation of solid dispersions, lyophilisation method was found to be the best method. The solid dispersions were further formulated as fast dissolving tablets by using newer super disintegrants were found to comply with the Indian Pharmacopoeial specifications. Among the newer super disintegrants croscarmellose sodium was found to be suitable disintegrant to enhance the rapid wettabiliy and dispersion of the tablets and thus improved the rate of dissolution. The other objectives of the investigation such has in vivo pharmacokinetic studies showed improved bioavailability of these formulations and accelerated stability studies indicated the stability of fast dissolving tablets. Thus the main aim and objective of the present investigation was fulfilled and achieved.