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Enhancement of solubility and dissolution rate of saxagliptine hydrochloride by solid dispersion technique

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ABSTRACT

Saxagliptine hydrochloride, PEG, polaxamer-407,ethyl cellulose were prepared to study the dissolution of sparingly water soluble Saxagliptine hydrochloride drug. solid dispersion of Saxagliptine hydrochloride were prepared using different ratios of PEG 6000 & Polaxamer-407.Some of the practical aspects to be considered for the preparation of solid dispersion such as selection of polymers ,methods of preparation solubility of drug and dissolution study of drug in solid dispersion are also discussed. The present research provides a there is increase in solubility of Saxagliptine hydrochloride and also solid dispersion complex of drug was giving better dissolution profile as compared to other solid dispersions this imporove bioavailability. FT-IR , shows the compatability of drug & carrier.

Keywords- solid dispersion, solubility enhancement, dissolution rate

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INTRODUCTION[6,8,11]

Solid dispersions can be defined as molecular or amorphous mixtures of poorly water soluble drugs in hydrophilic carriers in which the polymer properties play an important role in the drug dissolution profile. It has been estimated that 40% of new chemical entities being discovered are poorly water-soluble. With recent advances in screening methods for identifying potential drug candidates, an increasing number of poorly water-soluble drugs have been identified as potential therapeutic agents. Unfortunately, these drugs have poor bioavailability due to their poor solubility. This has limited the commercial potential of these drugs. The solid dispersion technique is one of the most efficacious to improve the bioavailability of drugs with low water solubility. Among the important factors increasing the solubility of drugs in solid dispersions, particle size reduction, reduced agglomeration, improved wettability and solubility, or dispersion of the drug as micro-fine crystals, amorphous materials or in a molecular form must be mentioned. These formulations offer many advantages over others and the most relevant are the lower cost of the adjuvants and the feasible industrial application.

Solid dispersion in an inert carrier or matrix of solid state prepared mainly by the melting (or fusion) and solvent evaporation methods. The melting method involves heating a physical mixture of an active agent and a carrier until melted, followed by rapidly solidifying under vigorous mixing, resulting in super saturation of the drug by instantaneous solidification. On the other hand, the solvent evaporation method involves dissolving a physical mixture of two or more chemicals in a common solvent, followed by evaporation of the solvent. The proper selection of solvent and its removal rate are crucial in determining the quality of the final dispersion. The release mechanism of drug from a variety of solid dispersions depends on the physical properties of carriers as well as drug substances and preparation methods.

MATERIALS AND METHODS

Materials

Saxagliptine was recieved from NEXA lab, All other materials used were of pharmaceutical or analytical grade.

Preparation of solid dispersion by solvent evaporation method[1]:

Required amount of Saxagliptine hydrochloride was dissolved in 20 ml of acetone. Accurately weighed carrier corresponding to different drug: carrier ratio by weight was dispersed in drug solution. Then the solvent was allowed to evaporate completely. The resulting solid mass was then pulverized in a mortar to get dry free-flowing powder. The powder was passed through a#40 mesh sieve. The resulting mass was transferred to desiccators containing silica and

stored until completely dry. Solid dispersion of Saxagliptine hydrochloride with polymers in the ratio (1:1:1, 1:3:3 and 1:5:5 resp.) was prepared.

Table 1: Formulation plan of Saxagliptine hydrochloride solid dispersions

INGREDIENTS	SSD1	SSD2	SSD3
DRUG:PEG6000:POLO-407 (A)	1:1:1	1:3:3	1:5:5
DRUG:PEG6000:ETHYLE CELLULOSE (B)	1:1:1	1:3:3	1:5:5

Preformulation study:

Solubility[12]:

Solubility is defined as the amount of substance that passes into solution to achieve a saturated solution at constant temperature and pressure. Solubility are expressed in terms of maximum volume or mass of the solute that dissolve in a given volume or mass of a solvent. Pharmacopoeias give solubility's in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid, or one part by volume of a liquid.

Saxagliptine is a white to light yellow or light brown powder. It is soluble in polyethylene glycol 400, acetone, acetonitrile, ethanol, isopropyl alcohol, methanol; sparingly soluble in water and slightly soluble in ethyl acetate.

Melting point[10] :

Melting point apparatus:-

1. Insert the capillary tube containing the sample into a slot behind the view finder of a melting point apparatus. There are usually three slots in each apparatus, and multiple melting points can be taken simultaneously after gaining experience with the technique.
2. Turn on the apparatus and adjust the setting to an appropriate heating rate. The rate of heating is often experimental and should be adjusted by careful monitoring of the thermometer on the apparatus.
3. Look through the view finder to see a magnified view of the sample in the apparatus, which should be illuminated.
4. If the expected melting point of the compound is known, heat at a medium rate to 20oC20oC below the expected melting point, then slow the rate of heating such that the temperature increases no more than10C1oC **every 30 seconds**.

   The temperature must be incremental as the melting point is approached so the system can reach equilibrium, making the thermometer temperature an accurate gauge of the solid's true temperature.
5. If the expected melting point of the compound is NOT known, heat the sample at a medium rate the entire time and determine an approximate melting point. Repeat the process with a fresh sample after allowing the apparatus to cool and use the recommendations in prompt 4 to perform a more careful assessment of the melting point. .
6. The solid may be approaching its melting point if the solid is seen pulling away from the walls of the tube to form a cone of solid, which is called "**sintering**." Melting will normally occur within a few degrees of this point. The solid may also shrink or compact before melting.
7. Record the first temperature of the melting range with the appearance of the first visible drop of liquid. At first it may seem as if the sides of the solid glisten, and the temperature should be recorded when a droplet is seen on the side or bottom of the tube.

   Record the temperature reading to the nearest degree. Although some thermometers may read to greater precision, the imperfect heat transfer between the metal block and sample leaves the error larger than 0.1oC0.1oC.
8. Record the second temperature of the melting range when the entire sample has just melted, which occurs when all portions of the opaque solid have turned to a transparent liquid.
9. If another melting point trial is to be performed directly after the first, the metal block should be rapidly cooled to at least 20oC20oC below the next melting point by touching it with wet paper towels or cooling it with a jet of air.

Obesrvation :- The melting point of Saxagliptine was found to be 105° c

Compability study :-

Infrared spectroscopy (IR)[11]:

Pressed pellet technique – In this technique, a small amount of finely ground solid sample of Saxagliptine is mixed with 100 times its weight of potassium bromide and compressed into a thin transparent pellet using a hydraulic press. These pellets are transparent to IR radiation and it is used for drug and carrier interaction.

% Practical Yield:

Percentage practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine %practical yield (PY) from the following equation.

$$PY(\%) = \frac{\text{Practical yield}}{\text{theoretical yield}} \times 100$$

Drug content [1,14]:

20 mg of solid dispersions were weighed accurately and dissolved in 20 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 212 nm by UV spectrophotometer. Then drug content was calculated for all batches using the equation as follows:
Drug content= Absorbance X Dilution Factor X Solvent

***In-Vitro* dissolution study [2.13]:**

Dissolution studies were performed assuring sink condition according to the basket method (USP) using USP XXIII apparatus type-II (electrolab TDT-O9T). The dissolution medium was 900 ml 0.1N HCl kept at 37°C ± 0.5°C. The solid dispersions containing 50 mg of Saxagliptine hydrochloride was taken in a muslin cloth and tied to the rotating basket. Kept in the basket of dissolution apparatus, the basket was rotated at 100 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 210.00 nm using Shimadzu-1800 UV-visible spectrophotometer. The samples withdrawn were replaced by fresh buffer solution. Each preparation was tested in triplicate and then mean values were calculated.

Infrared spectroscopy (IR):

IR spectroscopic studies were conducted by using perkinElmer Spectrum 65 FT-IR Spectrometer to determine possible drug: carrier interactions.

RESULT AND DISCUSSION

Solid dispersions of Saxagliptine hydrochloride were prepared by different methods using carriers like PEG 6000 and Poloxamer 407. In the present work, total 6 batches were prepared and their complete composition is shown in Table-2. All the Solid dispersions prepared were found to be fine and free flowing powders.

IR spectra of pure drug Saxagliptine hydrochloride, and optimized Solid dispersion of Saxagliptine hydrochloride were obtained which shows all the characteristic peaks of Saxagliptine hydrochloride and carrier was present in the Solid dispersion, thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion. The result of IR study shown in Figure No: 1.

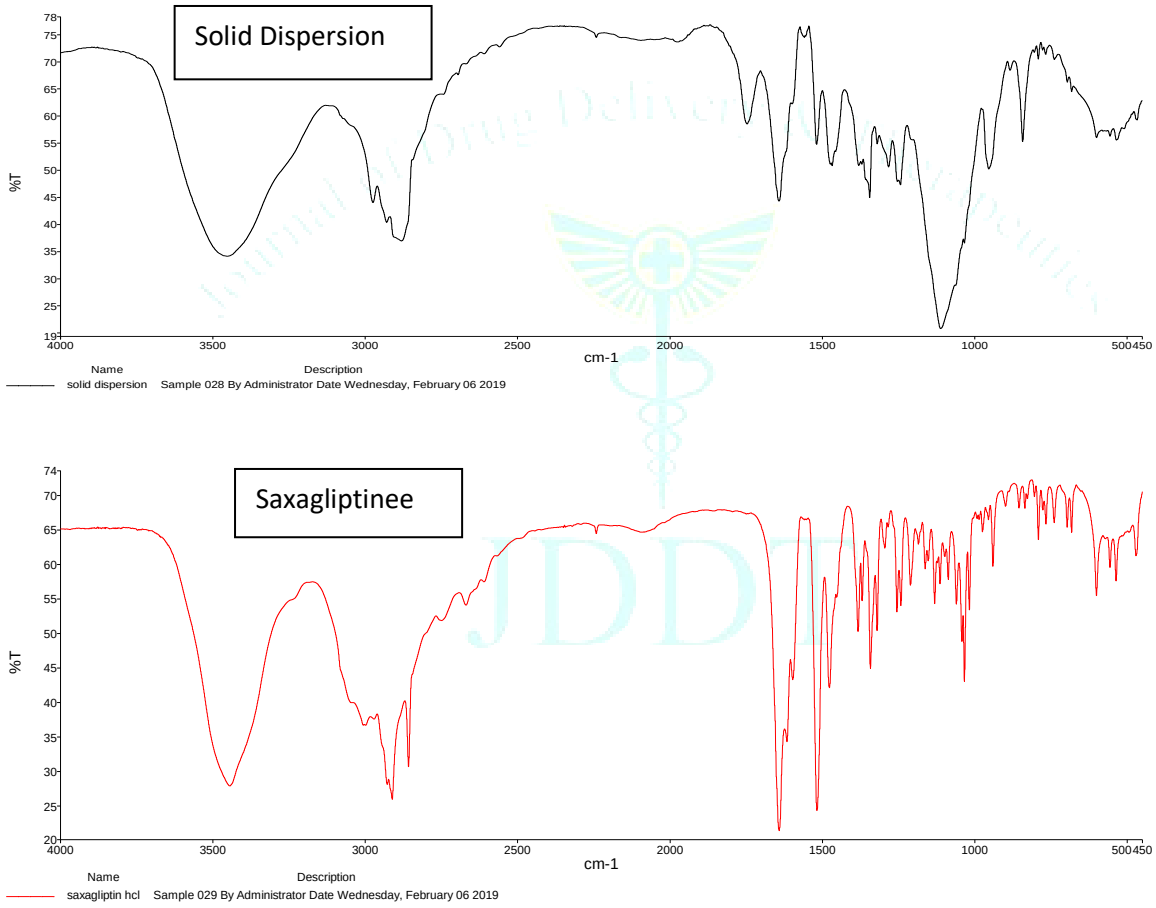

Fig. 1: IR Specta of Pure Saxagliptine HCL and Solid dispersion.

Table 2: Result of percentage yield, & Drug content of solid dispersion of Saxagliptine hydrochloride

CODE	% Yield	Drug content	Drug Release
SSD (A)1	85.06%	53.09	60.08
SSD (B)2	55.52%	47.90	52.09
SSD (A)3	64.18%	51.14	55.90
SSD (B)1	97.85%	68.15	70.88
SSD (B)2	83.42%	70.13	80.20
SSD (B)3	64.00%	57.13	60.12

CONCLUSION

The objective of the present study was to improve the solubility and dissolution behavior of the poorly soluble drug, Saxagliptine hydrochloride by solid dispersion technique using PEG 6000 and Ethyl cellulose as carrier. Solid dispersion of Saxagliptine hydrochloride prepared by a Solvent evaporation method showed significantly higher drug solubility in comparison with pure drug. FTIR studies showed no evidence of interaction between the drug and carrier.

Out of the 06 prepared batches SSD- B1 showed marked increase in the solubility as well as the dissolution when compared to pure drug. Thus it can be concluded that the solubility of the poorly soluble drug Saxagliptine hydrochloride can be improved by using solid dispersion technique and the carrier PEG 6000 & ethyl cellulose has increased the dissolution of the drug without any interaction.

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