Abstract

To enhance solubility and dissolution rate of Rivaroxaban by Inclusion complex with kneading method using Hydroxy propyl β cyclodextrin. The prepared Rivaroxaban inclusion complex were characterized in term of solubility and dissolution studies, Fourier transform infrared spectroscopy (FTIR). The aqueous solubility and dissolution rate of Rivaroxaban tablets was significantly increased. The dissolution rate of Rivaroxaban tablets was superior with compared to market sample.

Keywords: Rivaroxaban, Hydroxyl propyl β cyclodextrin, kneading method

Introduction

Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs.

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs). These are nonreducing, crystalline, water soluble, and cyclic oligosaccharides consisting of glucosemonomers arranged in a donut shaped ring having hydrophobic cavity and hydrophilic outer surface as illustrated in Figure 1. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin.

The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. Based on the structure and properties of drug molecule it can form 1 : 1 or 1 : 2 drug cyclodextrin complex as illustrated in Figure 4. Various technologies adapted to prepare the inclusion complexes of poorly water soluble drugs with cyclodextrins are described below.

Physical blending method
Kneading Method,
Co-precipitation technique,
Solvent evaporation technique,
Co-gridding technique,
Spray drying technique,
Lyophilization/Freeze-Drying Technique,
Microwave Irradiation Method,
Supercritical antisolvent technique
The Rivaroxaban is selected as the API as it is a novel first oral anticoagulant drug. Rivaroxaban is used to prevent blood clots from forming due to a certain irregular heartbeat (atrial fibrillation) or after hip or knee replacement surgery. It is also used to treat blood clots (such as in deep vein thrombosis-DVT or pulmonary embolus-PE) and to prevent the blood clots from forming again. Rivaroxaban has been shown more effective than the standard prescription of warfarin in reducing the likelihood of ischemic strokes in patients with atrial fibrillation or abnormal heart rhythms. Rivaroxaban has poor water solubility and belongs to BCS Class II drugs. Hence it has planned to enhance the solubility of drug and thereby dissolution of formulation, which may enhance the bioavailability of drug.

**Materials and Methods**

Rivaroxaban drug was obtained as gift sample from Symed Laboratories. Hydroxyl propyl β cyclodextrin was obtained as gift sample from BASF. Croscarmellose sodium, microcrystalline cellulose, hypromellose, magnesium stearate obtained as gift sample. Acetonitrile and phosphoric acid were taken from. Reagents were of analytical grade, and preparation of HPLC mobile phase was done with Millie-Q demineralized double-distilled water.

**Formulation of rivaroxaban inclusion complex**

The preparation method includes the dispersion of rivaroxaban in the hydroxyl propyl beta cyclodextrin at different ratios. The ratio of complexing agent in the optimized and finalized composition present in the ratio of 1:1 molar with respect to its solubility. The resulting inclusion complex was formulated in tablet with using other ingredient and dissolution carried out. The inclusion complex prepared by using kneading and physical mixer.

**Fourier transform infrared spectroscopy (FTIR)**

FTIR Spectroscopy is an important analysis technique which detects various characteristic functional groups in molecules of any matter. On interaction of an infrared light with the matter, chemical bonds would stretch, contract and bend and as a result each chemical functional group tends to absorb infrared radiation in a specific wavelength range regardless of the structure of the rest of the molecule. Based on this principle, functional groups present in composite materials are identified.

Fourier transform infrared spectroscopy (FTIR) has also been used to assess the interaction between complexing agent and Rivaroxaban molecules in the solid state. The chemical interaction between the drug and the complexing agent often leads to
identifiable changes in the infrared (IR) profile of mixture. However, some of the changes are very subtle requiring careful interpretation of the spectrum.

**Solubility studies**

**Rivaroxaban solubility with Hydroxy propyl beta cyclodextrin were measured as follows**

Saturation solubility study was done to determine the solubility of drug. Drug solubility studies were performed by adding excess amounts of drug to solution having Acetate Buffer pH 4.5. The mixture was equilibrate for 24 hrs at room temperature. It was then filtered through Whatman filter No.45. Analysed by UV-Spectrophotometrically at 248 nm, which was the absorption maximum wavelength of the drug. Saturation solubility study was done to determine the excess of solubility of drug.

**Dissolution study**

Dissolution studies of formulation of pure drug (Rivaroxaban) and complexation. Tablet forms were prepared and then to evaluate in vitro drug release profile. Dissolution Studies were carried out using method and condition given dissolution base from USFDA OGD with dissolution apparatus type II with dissolution Medium (Acetate buffer pH 4.5+0.4%SLS) at 37 °C ± 0.5 °C with 900ml volume. The paddle was rotated at 75 rpm. Samples of 6 ml were withdrawn at specified time interval (5, 10, 15, 20, 30, 45 minutes) and analysed spectrophotometrically at 248 nm using Shimadzu-1700 UV visible Spectrophotometer; the samples withdrawn were replaced by fresh media solution to maintain constant volume of medium.

**Results and Discussion**

**FTIR study**

FTIR spectrum of Rivaroxaban

![FTIR spectrum of Rivaroxaban](image1)

FTIR spectrum of Rivaroxaban + HP beta cyclodextrin (kneading)

![FTIR spectrum of Rivaroxaban + HP beta cyclodextrin (kneading)](image2)

The FTIR spectra of kneading (KN) showed a slight of peak with attenuated and decrease in peak intensities than those of pure Rivaroxaban indicating Physical interaction between HP-β- cyclodextrin and Rivaroxaban. The FT-IR of drug complex showed change in the major peak confirming formation of inclusion complex.
Solubility study

Saturated solubility of Rivaroxaban as shown in Table:

| Rivaroxaban: Excipient | Molar Ratio with Rivaroxaban | Formulation code | Method | Solubility (mg/ml) |
|------------------------|------------------------------|-----------------|--------|-------------------|
| Rivaroxaban            | 1:00                         | R1              | PM     | 0.01±0.007        |
|                        |                              | R2              | KM     | 0.01±0.006        |
|                        |                              | B6              | KM     | 0.45±0.014        |
|                        | 1:0.2                        | H1              | PM     | 0.25±0.022        |
|                        |                              | H2              | KM     | 0.29±0.015        |
|                        | 1:0.4                        | H3              | PM     | 0.38±0.014        |
|                        |                              | H4              | KM     | 0.42±0.018        |
| Rivaroxaban: HP β-Cyclodextrin | 1:0.6 | H5              | PM     | 0.47±0.026        |
|                        |                              | H6              | KM     | 0.50±0.021        |
|                        | 1:0.8                        | H7              | PM     | 0.60±0.017        |
|                        |                              | H8              | PM     | 0.69±0.025        |
|                        | 1:1.0                        | H9              | KM     | 0.75±0.022        |
|                        | 1:1.2                        | H10             | PM     | 0.70±0.018        |
|                        |                              | H11             | KM     | 0.74±0.024        |
|                        | 1:1.4                        | H12             | PM     | 0.67±0.023        |
|                        |                              | H13             | KM     | 0.72±0.014        |

Also found at 1:1 molar ratio found more solubility and no significant different in solubility at higher concentration. From above data Kneading method gives more solubility than physical mixer method.

Dissolution study

The dissolution profile of formulation of highest solubility (1:1) ratio inclusion complex

| Formulation code | Time | 5 min | 10 min | 15 min | 20 min | 30 min | 45 min |
|------------------|------|-------|--------|--------|--------|--------|--------|
| Market formulation | Mean ±SD | 49.2 ±5.23 | 73.7 ±4.02 | 82.4 ±2.65 | 90.1 ±2.70 | 95.6 ±1.60 | 96.2 ±1.62 |
| complex base formulation | Mean ±SD | 52.1 ±6.98 | 71.1 ±4.29 | 80.4 ±4.86 | 87.5 ±2.83 | 92.5 ±0.68 | 96.2 ±0.64 |
| Without complex based formulation | Mean ±SD | 20.2 ±7.13 | 29.4 ±6.42 | 37.5 ±5.20 | 41.5 ±2.97 | 47.6 ±2.82 | 51.4 ±0.78 |
Conclusion

• The highest improvement in solubility and in vitro drug release were observed in Inclusion complex prepared by kneading method with HP β-Cyclodextrin And prepared its tablets.

• The prepared tablets of Inclusion complex showed comparable and superior invitro drug release as compared to marketed formulation and without inclusion complex base formulation.

• FTIR spectra showed complex formation between the Rivaroxaban and HP β-Cyclodextrin.

• Hence, it was concluded that a Inclusion complex system of Rivaroxaban with HP β-Cyclodextrin a method of enhancing dissolution and Solubility.

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