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Formulation, Development and Evaluation of Rivaroxaban Tablets by using Solubility Enhancement Technique

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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 glucose monomers 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

Figure 1: Molecular structure and molecular shape of cyclodextrine

Figure 2: Drug cyclodextrin complexes

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 there by 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^{2,3}

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^{2,3}

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 data 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 + HP beta cyclodextrin (kneading)

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- cy-

clodextrin 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
Rivaroxaban: HP β-Cyclodextrin	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
	1:0.6	H5	PM	0.47±0.026
		H6	KM	0.50±0.021
	1:0.8	H7	PM	0.60±0.017
		H7	KM	0.67±0.024
	1:1.0	H8	PM	0.69±0.025
		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	49.2	73.7	82.4	90.1	95.6	96.2
	±SD	±5.23	±4.02	±2.65	±2.70	±1.60	±1.62
complex base formulation	Mean	52.1	71.1	80.4	87.5	92.5	96.2
	±SD	±6.98	±4.29	±4.86	±2.83	±0.68	±0.64
Without complex based formulation	Mean	20.2	29.4	37.5	41.5	47.6	51.4
	±SD	±7.13	±6.42	±5.20	±2.97	±2.82	±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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