

DISSOLUTION ENHANCEMENT OF POORLY WATER-SOLUBLE DRUG BY CYCLODEXTRINS INCLUSION COMPLEXATION

A. A. MENDHE, R. S. KHARWADE, U. N. MAHAJAN

Ambe Durga Education Society's, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur
Email: rohinismore@gmail.com

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ABSTRACT

Objective: Solubility of a drug is an important property that mainly influences the extent of oral bioavailability. Enhancement of oral bioavailability of poorly water-soluble drugs is the most challenging aspects of drug development. It is very important to find appropriate formulation approaches to improve the aqueous solubility and bioavailability of poorly aqueous soluble drugs. Ezetimibe is a new lipid lowering agent in the management of hypercholesterolemia. The drug is water-insoluble, lipophilic, and highly permeable according to the pharmaceutical classification system. Therefore, the bioavailability of ezetimibe may be improved by increasing its solubility.

Methods: In present work solubility of ezetimibe was increased with inclusion complexes by a different technique like physical mixture, co-grinding and modified kneading method. The physical properties of the prepared inclusion complex of ezetimibe were characterised by Differential scanning calorimetry (DSC), X-ray diffraction spectroscopy (XRD), Fourier transform infra-red spectroscopy (FTIR) and *in vitro* dissolution studies.

Results: From the dissolution studies of ezetimibe with HP- β -cyclodextrin(1:1 and 1:2), we conclude that the prepared complexes of ezetimibe with HP- β -cyclodextrin (1:2) by modified kneading method showed higher release i.e. 88.35% in 60 min. than in (1:1) 76.75% in 60 min. So, ezetimibe with HP- β -cyclodextrin (1:2) inclusion complex was used to formulate tablet by direct compression method.

Conclusion: From the dissolution data of formulated tablets was observed that drug release was more in tablet dosage form as compared to plain ezetimibe and especially formulation in a ratio of 1:2 was found the promising result. Also from one-month stability data shows no significant change compared to the initial result.

Keywords: Ezetimibe, Cyclodextrin complex, Solubility enhancement, HP- β -cyclodextrin

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INTRODUCTION

The rate of absorption and bioavailability of poorly water-soluble drugs is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Many technological methods of enhancing the dissolution characteristics of slightly water soluble drugs are particle size reduction, solid dispersion, nanosuspension, supercritical fluid technology, cryogenic technology, solid dispersions and inclusion complexation [1]. Among the different techniques of solubility enhancement, complex inclusion techniques are one of the easiest and economical methods of selection which ultimately helps to increase the dissolution rate of the drug and its bioavailability.

Ezetimibe, a poorly water-soluble drug and the oral delivery of the drug is frequently associated with low bioavailability. It is used as an anti-hyperlipidaemia drug in the management of hypercholesterolemia, homozygous sitosterolemia (phytosterolemia). After oral administration, drug molecule is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (drug molecule-glucuronide) [2, 3].

Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α , β or γ respectively) obtained by the enzymatic degradation of starch. These are torus shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs [4, 5]. Cyclodextrins are able to form inclusion complexes with poorly water-soluble drugs. The formation of the inclusion compounds greatly modifies the physical and chemical properties of the guest molecule, mostly in terms of water solubility. This is the reason why cyclodextrins have attracted much interest in many fields, especially pharmaceutical applications: because inclusion compounds of cyclodextrins with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions [6, 7].

The objective of present study was to prepare inclusion complexes of ezetimibe with cyclodextrins by different methods such as

physical, kneading and co-evaporation, precipitation method and increase the solubility of Ezetimibe for improvement of dissolution rate and bioavailability of the drug.

MATERIALS AND METHODS

Materials

Ezetimibe was a gift sample from Apollo Life Sciences Pvt. LTD, Mumbai India. β -cyclodextrin and H β -cyclodextrin was purchased from Roquette India Pvt. LTD, Mumbai. All other reagent and chemicals were analytical grade.

Instruments

Tablet compression machine: karnavati Mumbai, India

USP tablet dissolution apparatus II(paddle): Electrolab (TDT-08L), Pvt, Ltd, Mumbai,

Fourier Transform Infra-Red Spectrophotometer: Bruker Alpha, ATR model, Mumbai, India.

UV spectrophotometer: Shimadzu 1800, Japan

Differential scanning calorimetry: Mettler DSC 1 Star System, Mettler Toledo, Switzerland

X-ray ditractometry: X'pert Pro PANalytical India.

Stability Chamber: Remi, Mumbai India.

Methods

Phase solubility studies

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of ezetimibe was added to the screw capped vials containing 60 ml of aqueous carrier solution (β -Cyclodextrin and HP- β -Cyclodextrin) at various concentrations and placed on an orbital shaker and agitated

at room temperature for 72 h. After equilibrium, the solutions were carefully filtered through whatman no. 41 filter paper and after appropriate dilution; solutions were analysed at 231 nm by using UV-visible spectrophotometry [8].

Preparation of inclusion complexes of ezetimibe with β -cyclodextrin and HP- β -cyclodextrin

Physical mixture

The physical mixtures of ezetimibe with cyclodextrin were prepared by simple mixing using a spatula. This resulting mixture was sieved through a 80 mesh screen [10, 12]. The composition of the physical mixture is given in table 1.

Co-grinding complex

The required amount of ezetimibe and carriers were taken in a mortar pestle and grind for 45 min until a homogeneous complex was obtained. This resulting complex was sieved through an 85 mesh screen. The powder was stored in a screw cap container at room temperature [10, 12]. The composition of co-grinding is given in table 1.

Modified kneading method

Inclusion complexes were prepared by modified kneading technique. Ezetimibe and polymer were dissolved in ethanol and water in a proportion of 50:50, then the mixture were kneaded for 45 min and the slurry were obtained, the flask kept on the water bath till ethanol get evaporated and then resultant slurry were kept in deep freezer for 24 h and then freeze complex were dried by freeze dryer. The operating parameters like -40 °C, and 4 kg/test cycle pressure to be maintained [10, 12]. The composition of modified kneading method is given in table 1.

Table 1: Composition for physical mixture/co-grinding/modified kneading method

S. No.	Physical mixture/co-grinding/modified kneading method	Drug: polymer
1	Ezetimibe: β -Cyclodextrin	1:1
2	Ezetimibe: β -Cyclodextrin	1:2
3	Ezetimibe: HP- β -Cyclodextrin	1:1
4	Ezetimibe: HP- β -Cyclodextrin	1:2

Analysis of drug content

The content of ezetimibe in each physical mixture, co-grinding and modified kneading method of inclusion complexes was determined using UV spectroscopy. Accurately weighed physical mixture, co-grinding and modified kneading method inclusion complexes equivalent to 10 mg of ezetimibe was transferred to 100 ml volumetric flask containing 40 ml of ethanol and dissolved. The volume was made up to 100 ml with water. The solution was filtered through 0.45 μ m membrane filter paper. One ml of this solution was diluted 10 times with the same solvent and the absorbance was measured at 231nm [12, 14].

Characterization of inclusion complexes

Fourier transform infra-red spectroscopy (FTIR)

The IR spectrum of ezetimibe, β -cyclodextrin, HP- β -cyclodextrin and the physical mixture, co-grinding complex and modified kneading complex with β -cyclodextrin and HP- β -cyclodextrin were recorded in the stretching frequency range of 450 to 4000 cm^{-1} [14]. The samples were evaluated by ATR model.

Differential scanning calorimetry (DSC)

The DSC thermograms of ezetimibe, β -cyclodextrin, HP- β -cyclodextrin and the physical mixture, co-grinding complex and modified kneading complex with β -cyclodextrin and HP- β -cyclodextrin were recorded. The samples were separately sealed in aluminium cells and set in Perkinelmer (pyris 1) DSC. The thermal analysis was performed in a nitrogen atmosphere over a temperature range of 50 °C to 250 °C [14].

X-ray diffraction spectroscopy

The X-ray diffraction pattern of ezetimibe, β -cyclodextrin, HP- β -cyclodextrin and the physical mixture, co-grinding complex and modified kneading complex with β -cyclodextrin and HP- β -cyclodextrin were recorded from 5 to 100 °C at an angle 2θ using diffractometer system [14].

Dissolution rate studies

Dissolution studies were performed separately in 900 ml water with 0.25% sodium lauryl sulphate maintained at 37 \pm 0.5 °C using USP XXII type II dissolution test apparatus at a speed of 50 rpm. The physical mixture or inclusion complexes, equivalent to 10 mg of ezetimibe was taken for dissolution studies. Samples of 10 ml were withdrawn at regular intervals and replaced the same with fresh dissolution medium. The samples were estimated for the amount of dissolved by measuring their absorbance at 231 nm [12, 14]. The amount of released was calculated and plotted against time and compared with the pure drug. (fig. 11 and 12).

Preparation of tablets of inclusion complexes

The optimised modified kneading complex was formulated in tablets containing the equivalent to 10 mg of ezetimibe inclusion complexes were prepared by direct compression. The blend was compressed on a 10 station rotary machine using round shaped, concave punches [22, 23]. The composition of tablet is given in table 2.

Table 2: Composition of tablet formulation

Ingredients	Quantity (mg)
Modified kneading complex (1:2 HP- β -Cyclodextrin)	76
Microcrystalline cellulose	62
Magnesium stearate	2
Total	140

Evaluation of powder blend

The powder blend was evaluated for flow properties. Different tests that were carried out are bulk density, tapped density, compressibility index, and hausner ratio.

Evaluation of tablets

The hardness of the tablets was evaluated using the pfizer hardness tester. The friability of tablets for each batch was determined using automated USP roche friabilator. The tablets were subjected to tests like the uniformity of drug content, and variation weight tests single dose preparation as per US Pharmacopeia (USP) [22, 23].

In vitro dissolution study

Dissolution studies were performed separately in 900 ml of pH 1.2, pH 6.8 and water with 0.25 % sodium lauryl sulphate maintained at 37 \pm 0.5 °C using USP XXII type II dissolution test apparatus at a speed of 50 rpm. The sample (10 ml) was withdrawn at regular time intervals and replaced the same with fresh dissolution medium. The samples were estimated for amount of dissolved by measuring their absorbance at 231 nm [22, 23]. The amount of released was calculated and plotted against time (fig. 11 and 12)

Stability studies

The optimised formulation was kept for short-term stability study. The conditions for stability were 30 \pm 2 °C room temperature and relative humidity of 65% RH \pm 5% RH. All tablets were suitably packed in a group of 10 in aluminium foil. [15] At the end of one month the sealed tablets were opened and evaluated.

Statistical analysis

All analyses of data were performed with a statistical software package (SPSS 13, USA). The results are expressed as means and standard deviations. Comparative statistical studies on the inclusion complex and dissolution rate were performed by ANOVA.

RESULTS AND DISCUSSION

Phase solubility studies

The phase solubility studies were performed to determine stoichiometric proportions of ezetimibe and carrier's β -cyclodextrin and HP- β -cyclodextrin. The effects of polymers concentration at room temperature on solubility are shown in (fig. 1).

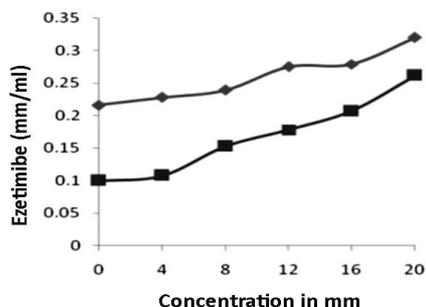


Fig. 1: Concentration of (-♦-) β -cyclodextrin and (-■-) HP- β -cyclodextrin carriers on solubility of ezetimibe[mean \pm SD, n= 3]. Error bars were omitted for clear presentation

The plot of drug solubility against polymer concentrations at room temperature indicated a linear relationship between drug and polymer solution. The ezetimibe and carriers β -cyclodextrin and HP- β -cyclodextrin is $r^2 = 0.946$, $r^2 = 0.968$ respectively. Which indicated that 1:1 (Ezetimibe: β -CD) and (Ezetimibe: HP- β -CD) inclusion

complex formed in solution. The value of stability constant (K_s) for complexes (Ezetimibe: β -CD) and (Ezetimibe: HP- β -CD) at 37 ± 0.5 °C, were 241.59 M^{-1} and 926.99 M^{-1} respectively. It is reported that cyclodextrin-drug complexes with the values of K_s in the range of 200 to 5000 M^{-1} show improved dissolution properties.

Evaluation of complexes

Analysis of drug content

The percentage of drug content of the physical mixture, co-grinding complex and modified kneading complex are shown in table 3.

Fourier transform infra-red spectroscopy (FTIR)

Fourier transform infrared spectroscopy has been used to assess the interaction between the carrier and drug molecule. The FTIR spectrum of ezetimibe, HP- β -cyclodextrin and inclusion complex prepared by attenuated total reflectance. FTIR spectra are shown in (fig.2,3,4). In IR spectra of ezetimibe the O-H stretching in alcohols occurs at 3239.72 cm^{-1} , the C-H stretching in alkanes at 2909.49 cm^{-1} , the C=O stretching in carboxylic acids occurs at 1714.12 cm^{-1} , the C-N stretching in amine occurs at 1217.03 and the C-F stretching in alkyl halides occurs at 1066.65 cm^{-1} , the C=C stretching in benzene ring occurs at 1508.93 . In IR spectra of HP- β -cyclodextrin the O-H Stretching in free hydroxyl occurs at 3401.06 cm^{-1} , the C-H Stretching in Alkanes occurs at 2929.89 cm^{-1} , the C=O stretching in ethers occurs at 1653 cm^{-1} , the C-O stretching in ethers occurs at 1032.36 cm^{-1} . In IR spectra of inclusion complex the O-H stretching in alcohols occurs at 3287.40 cm^{-1} , the C=O stretching in carboxylic acids occurs at 1729.80 cm^{-1} , the C-C stretching in aromatics occurs at 1508.02 cm^{-1} , the C-H stretching in aromatic occurs at 1397.07 cm^{-1} , the C-F stretching in alkyl halides 1027.29 cm^{-1} .

Table 3: Results of drug content with β -CD and HP- β -CD

Methods	Ratio	Drug content	
		Ezetimibe: β -CD	Ezetimibe: HP- β -CD
Physical Mixture	1:1	96.10 \pm 0.06	98.00 \pm 0.12
	1:2	97.35 \pm 0.15	98.50 \pm 0.05
Co-grinding Complex	1:1	95.17 \pm 0.12	97.41 \pm 0.10
	1:2	96.15 \pm 0.08	97.39 \pm 0.04
Modified Kneading Method	1:1	97.80 \pm 0.05	98.88 \pm 0.08
	1:2	98.55 \pm 0.08	99.15 \pm 0.07

[mean \pm SD, n= 3]

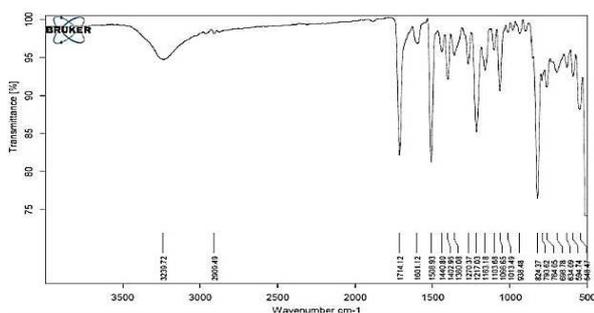


Fig. 2: FTIR spectrum of ezetimibe

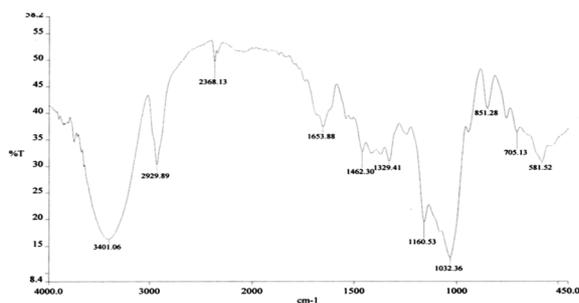


Fig. 3: FTIR spectrum of HP- β -cyclodextrin

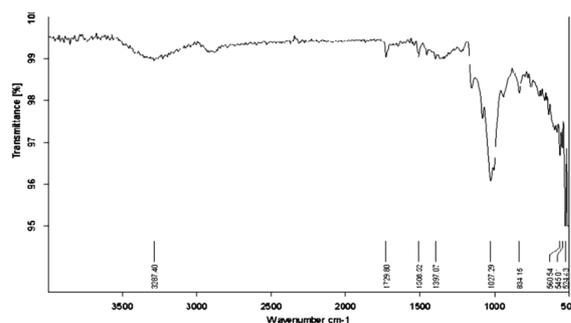


Fig. 4: FTIR spectrum of the inclusion complex prepared with HP- β -CD by modified kneading method (1:2)

Differential scanning calorimetry (DSC)

The DSC thermogram of ezetimibe, HP- β -cyclodextrin and its complex prepared by modified kneading method as shown in (fig. 5, 6, 7) respectively. The DSC curve of ezetimibe exhibited a sharp endothermic peak at 163.66 °C corresponding to its melting point. The DSC curve of HP- β -cyclodextrin showed a broad endothermic peak at 120.35 °C. The heat content of Ezetimibe was found to be -178.32 mJ and for HP- β -cyclodextrin it was -748.21 mJ respectively. The melting point and heat content of modified kneading complex of ezetimibe with HP- β -cyclodextrin in the ratio (1:2) were found to be 160.13 °C and -3.37 mJ .

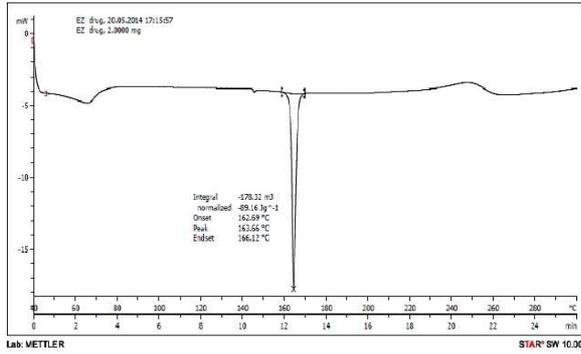


Fig. 5: DSC thermogram of ezetimibe

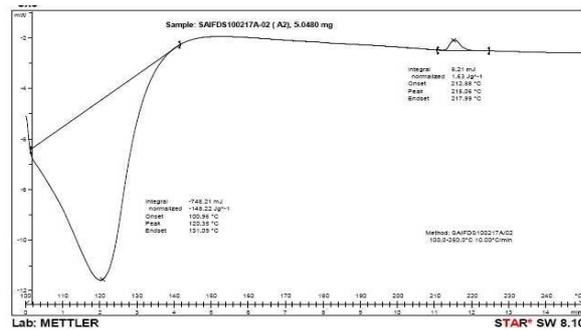


Fig. 6: DSC thermogram of HP-β-cyclodextrin

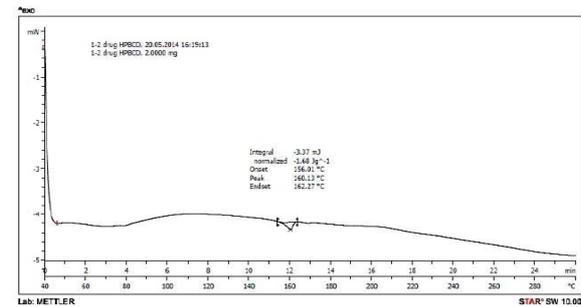


Fig. 7: DSC thermogram of the inclusion complex prepared with HP-β-CD by modified kneading method (1:2)

peaks because of its amorphous nature. The X-ray diffraction pattern of modified kneading method of ezetimibe with HP-β-cyclodextrin showed less intense and highly diffused peaks.

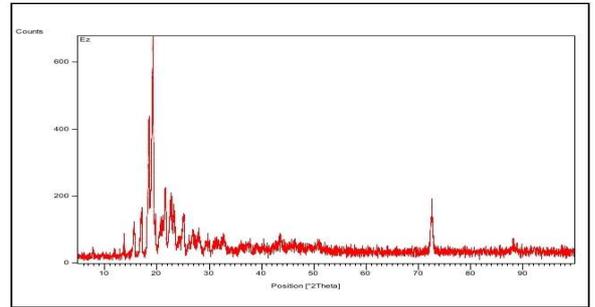


Fig. 8: XRD of ezetimibe

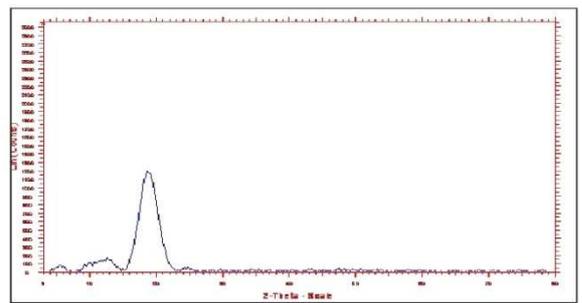


Fig. 9: XRD of HP-β-cyclodextrin

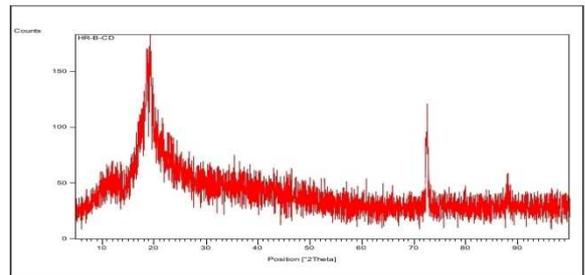


Fig. 10: XRD of the inclusion complex prepared with HP-β-CD by modified kneading method (1:2)

X-ray diffraction (XRD)

Powder X-ray diffraction spectroscopy has been used to assess the degree of crystallinity of the given sample. XRD patterns are shown in (fig. 8, 9, and 10). The X-ray diffraction pattern of ezetimibe exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of ezetimibe. HP-β-cyclodextrin showed diffused

In vitro dissolution studies of modified kneading method

In order to study the release profile of ezetimibe and modified kneading complex was subjected to dissolution studies in (a) Distilled water, (b) pH 1.2 and (c) pH 6.8. The results are as shown in (fig. 11, 12)

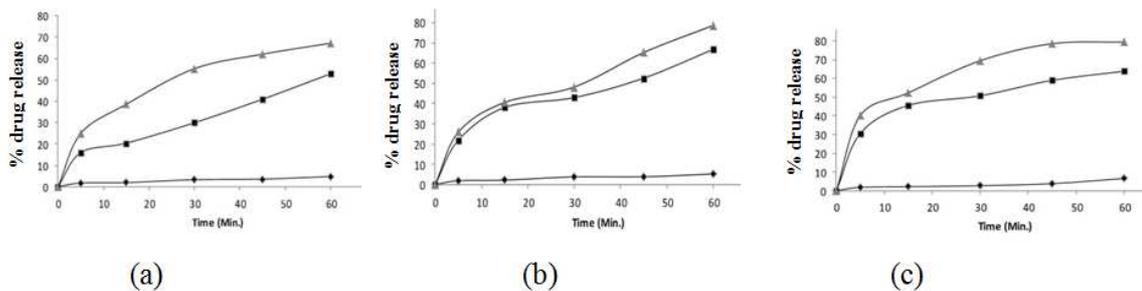


Fig. 11: Dissolution profile of (-□-) ezetimibe, modified kneading complex of ezetimibe with β-CD 1:1 (-○-) and modified kneading complex of ezetimibe with β-CD 1:2 (-▲-) [mean±SD, n= 3]. Error bars were omitted for clear presentation

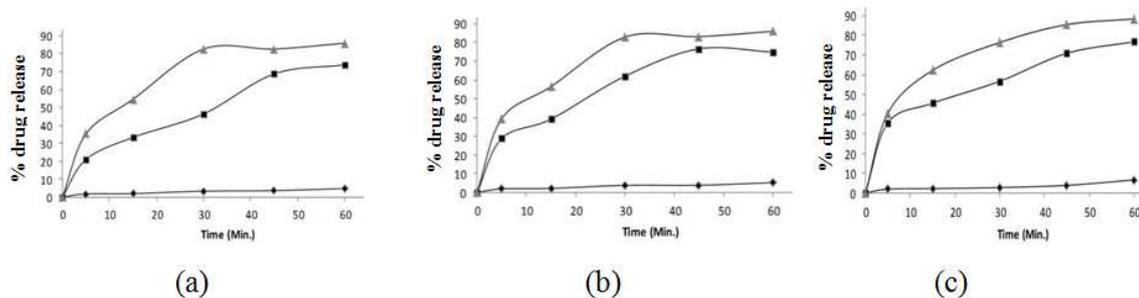


Fig. 12: Dissolution profile of (-□-) ezetimibe, modified kneading complex of ezetimibe with HPβ-CD 1:1 (-■-) and modified kneading complex of ezetimibe with HPβ-CD 1:2 (-▲-) [mean±SD, n= 3]. Error bars were omitted for clear presentation

In order to investigate the drug release from the prepared inclusion complex, *in vitro* dissolution study carried out in distilled water, pH 1.2 and pH 6.8. The inclusion complex prepared with HP-β-cyclodextrin by modified kneading method (1:2) showed better drug release as compared to inclusion complex prepared with β-CD. The drug release rate of modified kneading method with HP-β-CD (1:2) was 82.58±0.28 in 30 min., 85.87±1.59 in 30 min and 88.45±0.90 in 45 min. in distilled water, pH 1.2 and pH 6.8 which is as shown in fig 11 and 12. Respectively. From the results of dissolution studies, the modified kneading method (1:2) prepared by using HP-β-cyclodextrin was selected for tablet formulation.

Pre-compression evaluation of tablet blend

The results of pre-compression evaluation of tablet blend are given in table 4.

Evaluation of tablet

Hardness, % friability, weight variation and drug content of tablet are given in table 5.

Table 4: Evaluation of inclusion complex tablet blend

Parameter	Result
Angle of Repose	25.78±0.11
Bulk density (g/ml)	0.43±0.05
Tapped density (g/ml)	0.46±0.02
% compressibility	12.76±0.35
Hausner ratio	1.06±0.04

[mean±SD, n= 3]

Table 5: Post compression evaluation of formulated tablet

Parameters	Results
Weight Uniformity (mg)	140±0.15
Friability (%)	0.5±0.03
Thickness (mm)	3.5±0.24
Hardness (Kg/cm ²)	3.8±0.08
Content uniformity	98.10±0.15
Disintegration time (min)	10.5±0.45

[mean±SD, n= 3]

Table 6: Results of stability study

Parameters	Result	
	Initial	After stability study
Hardness (kg/cm ²)	3.8±0.10	3.8±0.07
Friability (%)	0.5±0.39	0.5±0.45
Disintegration time	10.5±0.10	10.5±0.32
Dissolution	65.20% in Water	64.34% in Water
	85.13% in pH 1.2	83.25% in pH 1.2
	88.25% in pH 6.8	87.12% in pH 6.8
Drug content	98.10±0.15	97.05±0.17

[mean±SD, n= 3]

DISCUSSION

The solubility curve was classified as the AL type according to Higuchi and Connors shown that the apparent solubility of ezetimibe

Dissolution study of formulated tablet

The formulated tablets were subjected to dissolution study in distilled water, pH 1.2 and pH 6.8 results were shown in (fig. 13)

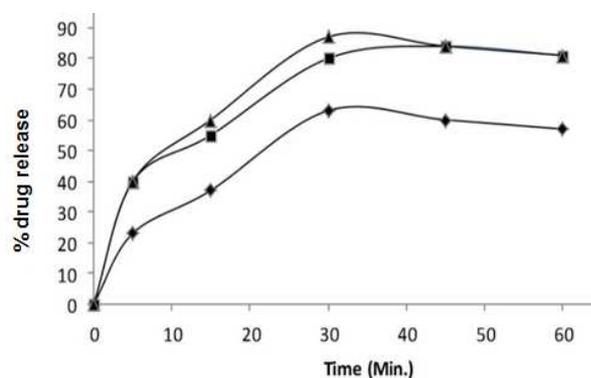


Fig. 13: *In vitro* drug release of ezetimibe from tablet formulation in (-□-) distilled water, (-■-) pH 1.2 and (-▲-) pH 6.8 [mean±SD, n= 3]. Error bars were omitted for clear presentation

From the fig. 13, it was observed that the drug release rate of formulation in distilled water, pH 1.2 and pH 6.8 was 65.20% in 30 min. and 85.13% in 45 min. and 88.25% in 30 min. respectively.

Stability study

At the end of one month, the formulation was tested for different parameters such as hardness, friability, disintegration time and dissolution. The results observed are reported in table 6.

increases linearly as a function of HP β-cyclodextrin over the entire concentration range and was the characteristic of AL type of curve [8], which suggests that water soluble complex was formed in solution. Percentage drug content of the complexes are shown in the

table and found within the range 96.10% to 99%. The maximum % drug content was found to be 99.15 % in modified kneading method.

The FTIR spectra of ezetimibe and HP β -cyclodextrin inclusion complexes showed the absence of the spectra of pure drug which indicates entrapment of drug into the cavity and confirms the complex formation. In DSC thermogram of modified kneading complex of ezetimibe with HP β -cyclodextrin in the ratio 1:2, the endothermic peak was reduced as compared to the ezetimibe. From the results of heat content, it can conclude that lower heat absorbed in the melting process of ezetimibe indicated increased solubility from modified kneading complex with HP β -cyclodextrin. When complexation of drug and HP β -cyclodextrin/ β -cyclodextrin is formed, the overall number of crystalline structures is increased. The final product sample shows less number as well as less intensity of XRD peaks. This shows that overall crystallinity of complexes was decreased and due to more amorphous nature the solubility was increased [12, 14]. From the result, it concludes that the inclusion complex prepared by modified kneading method of ezetimibe and HP β -cyclodextrin showed a reduction in peak intensity as compared to ezetimibe indicating the formation of an inclusion complex. The dissolution performance of inclusion complex by kneading method was increased as compared to pure ezetimibe, physical mixture and co-grinding complex in water, pH 1.2 and pH 6.8 in particular time course. This may be attributed to improved wettability of drug particles significant reduction particle size during formation of inclusion complex and intrinsically higher rate of dissolution of the selected soluble polymer, which could pull insoluble but finely mixed drug into the bulk of dissolution medium.

In pre-compression evaluation of tablet, the value of the angle of repose was found to be below 30 °C which indicates good flow property. The bulk density and tapped density value was found to be less than one. Similarly, the % compressibility value for all batches was less than 16% which also indicate that all batches of tablet blend have good flow property. Hardness, friability, weight variation, thickness, the disintegration time of tablet formulation were within acceptable limits and exhibited maximum release in distilled water and in phosphate buffer at pH 6.8. Hence formulation selected for stability study showed no significant changes in post compression evaluation parameter.

CONCLUSION

The present investigation revealed that ezetimibe can form an inclusion complex with β -cyclodextrin and HP- β -cyclodextrin in the solid state. The stoichiometry of complex formation is in 1:1 molar ratio with better stability constant. From these results, it can be assumed that the formation of the inclusion complex of ezetimibe with HP- β -cyclodextrin can increase the aqueous solubility of ezetimibe more than with β -cyclodextrin. The improved dissolution rate may be due to increasing insolubility, brought about by complexation, amorphizing power of HP- β -CD and mechanical treatment. From this evidence, it can be concluded that the aqueous solubility and dissolution rate of Ezetimibe can be significantly increased by forming an inclusion complex with HP- β -cyclodextrin. Further, inclusion complexes prepared by modified kneading method is found to be superior with respect to enhancement in aqueous solubility than those obtained by the physical mixture and co-grinding complex. From the dissolution data of formulated tablets was observed that drug release was more in tablet dosage form as compared to plain Ezetimibe and especially formulation in a ratio of 1:2 was found the promising result. Also from one-month stability data shows no significant change compared to the initial result.

CONFLICT OF INTERESTS

Declare none

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