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Studies on the Preparation, Characterization, and Solubility of 2-HP-β-Cyclodextrin-Meclizine HCl Inclusion Complexes

George SJ, Vasudevan DT

Department of Pharmaceutics, Amrita School of Pharmacy, AIMS Health Care Campus, Kochi, Kerala, India

Address for correspondence: *Dr. Deepa T Vasudevan; E-mail: drdeepatv@gmail.com*

ABSTRACT

Meclizine HCl is a poorly water-soluble drug having a very slow-onset of action. The effect of 2-hydroxypropyl-β-cyclodextrins and β-cyclodextrins on its aqueous solubility and dissolution rate was investigated. The phase solubility profile indicated that the solubility of Meclizine HCl was significantly increased in the presence of both 2-hydroxypropyl-β-cyclodextrin and β- cyclodextrin; an extend of increase being more for 2-hydroxypropyl-β-cyclodextrin. It was classified as A_L-type, indicating the 1:1 stoichiometric inclusion complexes. The complexes formed were quite stable. The solid complexes prepared by physical mixtures, kneading methods, and co-precipitation methods were characterized using differential scanning calorimetry and FTIR. An *in vitro* study showed that the solubility and dissolution rate of Meclizine HCl were significantly improved by complexation with 2-hydroxypropyl-β-cyclodextrin. Tablet formulation using 1:1 kneading complex of Meclizine HCl and 2-hydroxypropyl-β-cyclodextrin with drug equivalent to 25 mg was prepared by a direct compression method. A dissolution study of prepared tablets was performed in 0.5% SLS in water (pH 7.0). Almost 96% drug was released from the formulation at the end of 30min. A comparison study of prepared tablets was done with marketed a Meclizine HCl 25 mg conventional tablet. From the results of dissolution study, it was found that the prepared formulation was showing better release, which was statistically significant $P < 0.01$ than a marketed tablet (paired *t*-test). Only 54% drug release was observed from the marketed tablet at the end of 30 min. Hence this study concludes that the solubility enhancement of Meclizine HCl could be successfully achieved using the inclusion complexation technique.

Key words: 2-Hydroxypropyl-β-cyclodextrin, β-cyclodextrin, co-precipitation method, kneading method, phase solubility profile, Meclizine HCl

INTRODUCTION

Meclizine is an antihistamine. It blocks the effects of the naturally occurring chemical histamine in our body. Chemically, it is 1-(*p*-chloro-alpha-phenylbenzyl)-4-(*m*-methyl-benzyl)–piperazine dihydrochloride monohydrate. Meclizine is used to treat nausea, vomiting, and dizziness-associated with motion sickness. Meclizine may also be helpful in treating vertigo. Meclizine has CNS depressant, anticholinergic, antiemetic, antispasmodic, and local anesthetic effects in addition to antihistaminic activity. The drug depresses labyrinth excitability and conduction in vestibular-cerebellar pathways. The antiemetic and antimotion-sickness actions of the Meclizine result, at least in part, from its central anticholinergic and CNS depressant properties. Meclizine's antiemetic duration of action may last up to 24 h and has a

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half life of 6 h. It produces less drowsiness as compared to other antihistamines of its class and also has longer duration of action. Meclizine has a lag of 1 h in the onset of action hence should be taken 1 h prior to travel for protection against motion sickness.[1-3] This lag in the onset of action may be attributed to its poor solubility. The solubility of a poorly soluble drug can be altered in many ways, such as modification of drug crystal forms, addition of co-solvents, addition of surfactants, complexation with cyclodextrin, etc. Among these possibilities, the cyclodextrin approach is of particular interest. Meclizine HCl is very slightly soluble in water (0.261 mg/ml). In particular, Meclizine HCl exhibits very low solubility at pH values greater than 2.0. The poor solubility and wettability of Meclizine HCl give rise to difficulty in pharmaceutical formulations meant for oral or parental use. To overcome these difficulties, an increase in the aqueous solubility of Meclizine HCl is an important goal, hence in this investigation solubility enhancement of Meclizine HCl was tried with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and β-cyclodextrin (β-CD) to find out which among the two cyclodextrins was more effective in enhancing its solubility. Moreover, inclusion complexation of the Meclizine HCl was tried using cyclodextrin with the aim to improve its pharmaceutical properties like aqueous solubility and dissolution properties.

Cyclodextrin are cyclic (α-1,4)-linked oligosaccharides of α-d-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to the lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrin are not perfectly cylindrical molecules but toroidal or cone shaped. Based on this architecture, the primary hydroxyl groups are located on the narrow side of the cone shape, while the secondary hydroxyl groups are located on the wider edge. During the past two decades, cyclodextrin and their derivatives have been of considerable interest in the pharmaceutical field because of their potential to form complexes with a variety of drug molecules. Cyclodextrin are used to increase the solubility of water-insoluble drug through inclusion complexes formulation.[4-5] The hydrophobic cavity of cyclodextrin is capable of trapping a variety of molecules within to produce inclusion complexes. Many advantages of drugs complex with cyclodextrin have been reported in the scientific literature which includes increased solubility, enhanced bioavailability, improved stability, masking of bad test or odour, reduced volatility, transformation of liquid or gas into solid form, reduced side effect, the possibility of a drug release system, etc.[6-7] 2-Hydroxypropyl beta-cyclodextrin (HP β-CD) is modified beta-cyclodextrin (β-CD) having a high aqueous solubility (about 60%) and a proven safety profile, especially for parenteral use.[8] HP-β-CD is produced from β-CD by addition of propylene oxide to some of the hydroxyl groups of β-CD. This modification results in greater solubility of HP-β-CD and its complexes compared to β-CD.

The solid-state characteristics of the drug after preparation and during storage will depend on the processing variables as well as the characteristics of the system. When the objective of the formulation is to attain faster dissolution rates, the presence of high energy amorphous form of drug would improve the dissolution rate of drug and also on the ability of the cyclodextrin to form soluble complexes with the drug.[9-11] The performance of the product over the shelf life would depend on the ability of the cyclodextrin to prevent crystallization of the amorphous drug to its stable crystalline forms.[12] In this study, the complex of Meclizine HCl with HP-β-CD was prepared by using physical mixture, kneading method, and co-precipitation method at a 1:1 molar ratio.[13,14] The characterization of drug with HP-β-CD using DSC and FTIR, *in vitro* aqueous solubility and dissolution rate profile of complexes were performed.[15-17] Tablet formulation of Meclizine HCl using the 1:1 kneading complex of 2-hydroxypropyl-β-cyclodextrin with a drug equivalent to 25 mg was prepared using sodium starch glycolate as superdisintegrants, and Pearlitol SD 200 and Avicel PH102 as diluents, aspartame as sweetening agent, and lemon as flavour, by using a direct compression method. Evaluations of precompression and postcompression parameters were performed. A dissolution study of prepared tablets was performed in 0.5% SLS in water (pH 7.0). A comparison study of prepared tablets was done with marketed a Meclizine HCl 25 mg conventional tablet.

MATERIALS AND METHODS

Chemicals

Meclizine HCl, Sodium Starch Glycolate, Pearlitol SD 200, Avicel PH102, Aspartame, and Lemon were obtained as a gift sample from Unique Pharmaceutical Lab., Mumbai India. HP-β-CD and β-CD were from Signet Chemical Corporation Pvt. Ltd., Mumbai. All other ingredients and solvent used were of analytical grade.

Phase solubility studies

The phase-solubility technique permits the evaluation of the affinity between HP-β-CD and β-CD with Meclizine HCl in water. It gives not only the solubilising ability of CD's, but also the stability constant of the complexes by analysing the solubility curve. Phase solubility studies were performed according to the method reported by Higuchi and Connors.[18-20] This methodology was based

on the solubility variation of the guest molecule (drug) upon increase of the host molecule (β-CD/HP β-CD) concentration. Solubility studies were performed by taking excess of drug (100 mg) and added to 50 ml of distilled water containing varying concentration of β-CD (3–15 mM) and HP-β-CD (3–15 mM) in a 100 ml screw capped amber coloured bottles. The mixtures were shaken for 48 h on thermo-statistically controlled shaking water bath at 37 ± 1°. This amount of time is considered sufficient to reach equilibrium. Subsequently, the aliquots were withdrawn, using a syringe and samples were filtered immediately through a 0.45-μm membrane filter (PVDF) and approximately diluted.[21]

A portion of the sample was analyzed by a UV spectrophotometer (UV-1700, Shimadzu, Japan) at 232 nm against a blank prepared in the same concentration of cyclodextrin in water. The solubility experiments were performed in triplicate. The apparent stability constant (K_c) according to the hypothesis of 1:1 stoichiometric ratio of complex was calculated from the phase solubility diagrams using the following equation.[22]

$$K_{1:1} = \text{slope}/S_0 (1 - \text{slope})$$

The slope was obtained from the initial straight line portion of the plot of Meclizine HCl concentration against HP-β-CD and β-CD, so is the equilibrium solubility of Meclizine HCl in water.

Preparation of solid inclusion complexes

The following inclusion complexes of Meclizine HCl and HP-β-CD were prepared at 1:1 molar ratio.

Physical mixture

The physical mixture (PM) of Meclizine HCl and HP-β-CD in 1:1 molar ratio was prepared by mixing individually components that had previously been sieved through sieve no 60.

Kneading method

Meclizine HCl and HP-β-CD in a molar ratio of 1:1 was wetted with appropriate quantity of water to form a kneaded-like paste. Several hours of trituration and grinding of paste in a mortar result in evaporation of solvent. The kneading mass thus obtained is dried for 48 h and pulverized which results in formation of powder-like complex.

Co-precipitation method

Accurately weighed drug and HP-β-CD in a molar ratio of 1:1 were dissolved in 1:1 solution of methanol: water to get a clear solution. The resulting solution was stirred at ambient temperature until complete evaporation of the solvent occurred. The resulting solution were kept in desiccator for 48 h, and then grounded in a ceramic mortar for size reduction and passed through sieve # 100, which results in formation of a powder-like complex.

Differential scanning calorimetry

The samples were analyzed by *differential scanning calorimetry* (DSC) using a Mettler Toledo SR system. The samples (5mg each) were placed into pierced an aluminum container. The studies were performed under a static air atmosphere in the temperature range of 20–400°C at a heating rate of 10°C/min. The peak temperatures were determined after calibration with the standard.

Fourier transform infrared spectroscopy

Fourier transform IR spectra were recorded on FT/IR-4100 type A. The spectra were recorded for Meclizine HCl, HP-β-CD, physical mixture, kneaded and co-precipitation system. Samples were prepared in a KBr disc (2mg of the sample in 200mg KBr). The scanning range was 400–4000cm^{-1}, resolution was 4cm^{-1}.

In vitro dissolution studies

The dissolution patterns of the complexes were compared with those of a pure drug. The dissolution studies were performed according to the USP XXIII Dissolution apparatus (LABINDIA), Type-II (paddle). The sample corresponding to 25mg of Meclizine HCl was placed into hard gelatin capsules. The dissolution medium was 900 ml of 0.5% SLS in water (pH 7.0). The stirring speed of the paddle was 50 rpm, and the temperature was maintained at 37 ± 0.5°C. The samples (5 ml) were withdrawn at various time intervals, which was filtered through a 0.45 μm membrane filter (PVDF) and analyzed by a UV spectrophotometer at 232 nm.[23-25]

Formulation of tablets by direct compression method

All the ingredients in Table 1 were weighed and passed through # 60 mesh separately. Then, the ingredients were mixed and compressed into a tablet using 9.5 mm flat-faced punches on a 16 station rotary tablet machine (Cadmach, Manesty).

Evaluation of precompression parameters of powder blend

Micrometric properties of the powder blend for compression like angle of repose, bulk density, tapped density, % compressibility, and Hausner ratio were evaluated.[26]

Evaluation of postcompression parameters of tablets

The prepared tablets were evaluated for tablet hardness using a Dr. Schleuniger Tablet tester (Pharmatron), friability

Table 1: Formulae of fast dissolving tablets of binary system of Meclizine HCl

Ingredients	F1 (mg)
Eq. blend of Meclizine HCl	97.63
Pearlitol SD200	58.57
MCC (Avicel pH 102)	30
Sodium starch glycolate	4
Aspartame	1.5
Lemon flavor	1.5
Aerosil (0.4%)	0.8
Talc (3%)	6
Total	200 mg

of a sample of 20 tablets was measured using a Roche friabilator (Electrolab), the weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight, disintegration time of the tablet was measured in water (37±2° C) according to the disintegration test apparatus with a disk (Electrolab). Dissolution studies were carried out in 900 ml of 0.5% SLS in water (pH 7.0) by the USP paddle method at 50 rpm. Comparison of the dissolution profile of the prepared tablet was done with a marketed Meclizine HCl 25mg conventional tablet.[26,27]

RESULTS

Phase solubility study

The phase solubility profiles obtained for the complex formation between Meclizine HCl-β-CD system and Meclizine HCl-HP β-CD system are presented in Figure 1. This plot showed that the aqueous solubility of drug increase linearly as a function of HP-β-CD and β-CD concentration. The shape of solubility diagram represents linear host–guest correlation (A_L Type)[28,29] with a slope less than 1 indicating the formation of a 1:1 complex with respect to HP-β-CD and β-CD concentrations. The apparent stability constant, K_c, obtained from the slope of linear phase solubility diagram was found to be 370.53 M^{-1} for β-CD and 453.54 M^{-1} for HP-β-CD.[30] It was observed that the Meclizine HCl-HP-β-CD system shows greater solubility than the Meclizine HCl-β-CD system and this may be attributed to the fact that the contact surface and cavity size of HP-β-CD are higher than β-CD thus, HP β-CD is selected for further formulation and evaluation studies.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to identify the inclusion complex between the drug and HP-β-CD. Some evidence of inclusion complexation was

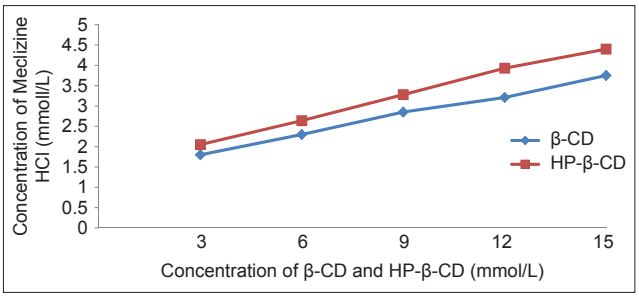

Figure 1: Phase solubility diagram of Meclizine HCl with β-CD and HP-β-CD

obtained from thermal analysis. When guest molecules were embedded in HP-β-CD cavities, their melting, boiling, or sublimation point generally could shift to a different temperature or disappear within the temperature range where HP-β-CD was decomposed. As seen from Figure 2, the DSC thermogram of Meclizine HCl alone showed a sharp endothermic peak at 225 °C, corresponding to the melting point of the drug, while HP-β-CD showed a very broad endothermic effect, which attained a maximum around 88.06 °C, due to the release of bound water in the cavity [Figure 3]. The endothermic peaks of Meclizine HCl (191 °C) and HP-β-CD (99.68 °C) observed in the physical mixture were significantly different from their endotherms in pure forms (lowering of the endothermic peak) indicating that complex formation has taken place only partially that also indicates reduction in drug crystallinity due to complexation [Figure 4]. The same was the case for the complex prepared by a co-precipitation method where endothermic peaks of Meclizine HCl (180.58°C) and HP-β-CD (99.68°C) were observed [Figure 5], which indicates complex formation is not complete but has taken place to a greater extent. The complete disappearance of the Meclizine HCl endothermic peak was observed for the inclusion complex prepared by the kneading method [Figure 6], since Meclizine HCl was contained within the cavity of the HP-β-CD ring molecule.[31] This demonstrated that an inclusion complex of Meclizine HCl could be obtained by the Kneading method.

Fourier transform infrared spectroscopy

IR spectrum of Meclizine HCl [Figure 7] is characterized by 3395.32cm^{-1} (–N– stretch), 3035.64cm^{-1} (CH = CH stretch aromatic), 2974.35cm^{-1} (C–H stretch aliphatic), 2365.49cm^{-1} (CH_2–CH_2), 1629.97cm^{-1} (C = C stretch), 1486.95cm^{-1} (C–N stretch), 1192.74cm^{-1} (C–Cl stretch). The IR spectrum of pure HP-b-CD [Figure 8] is characterized by prominent peaks at 3412cm^{-1} (O–H), 2929.13cm^{-1} (C–H), 1645.73cm^{-1} (H–O–H bending), 1032.28cm^{-1} (C–O–C). No significant alterations in the IR bands of the pure drug were detected in the physical mixture [Figure 9]. However, some of the

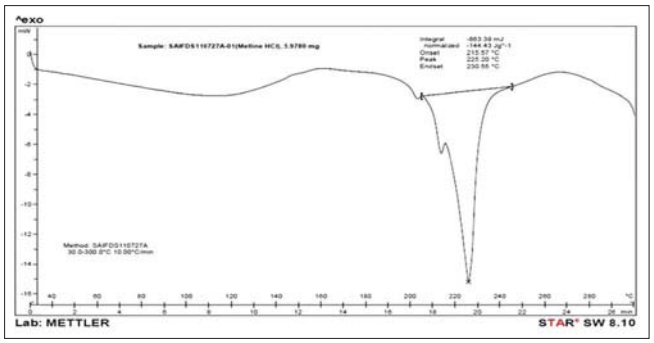

Figure 2: DSC thermogram of Meclizine HCl

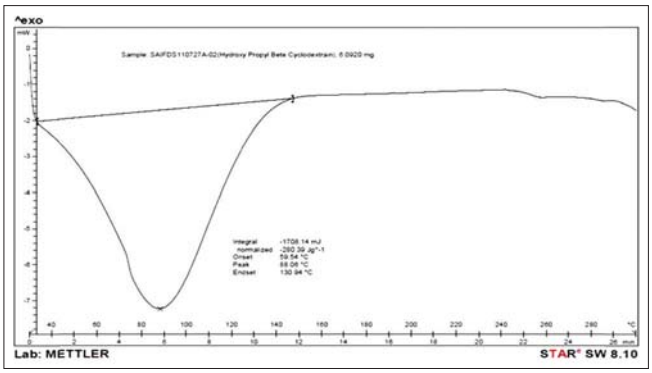

Figure 3: DSC thermogram of HP-β-CD

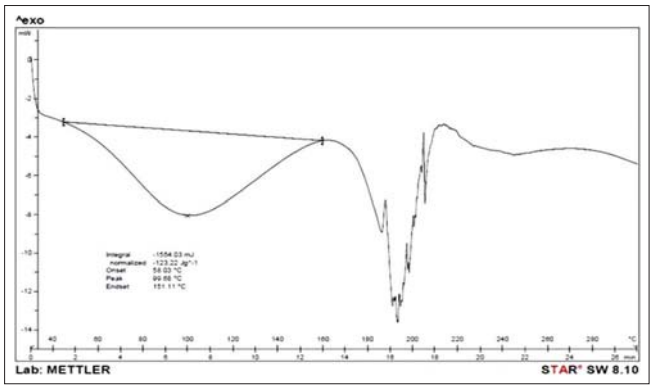

Figure 4: DSC thermogram of physical mixtures

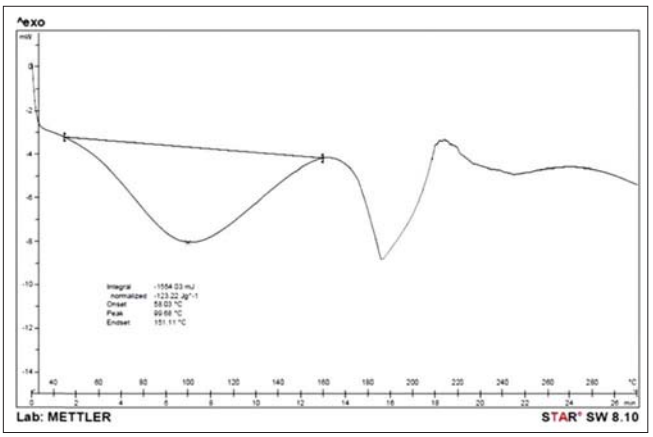

Figure 5: DSC thermogram of the co-precipitation complex

peaks of Meclizine HCl were slightly shifted and found to be attenuated. The broadening of peak was probably due to the restriction of bending and stretching vibration of the Meclizine HCl due to the HP-β-cyclodextrin cavity. The peak of –N– stretch was found to be disappeared or might be over lapped by O–H stretch of HP-β-CD. However, the IR spectrum of the physical mixture could be diagnosed as a superimposition of the bands of pure drug and HP-β-CD. Significant changes were recorded in the IR spectrum of the inclusion complex prepared by the kneading [Figure 10] and co-precipitation method [Figure 11]. Almost all peaks of Meclizine HCl were smoothened indicating a strong physical interaction between pure drug and HP-β-CD. However, the broad peak of O–H of HP-β-CD was consistently appeared in binary systems. The peak of HP-β-CD at 1645.73cm^{-1} due to water of crystallization was disappeared which might be because of the replacement of water molecules by Meclizine HCl inside the HP-β-CD cavity indicating the formation of the inclusion complex in the solid state. All the binary systems of Meclizine HCl-HP-β-CD did not show any new peaks, indicating noncovalent interaction in inclusion complex.[32]

Drug content

The HPLC method with a UV-detector was used to determine the drug content of the binary system of the HP-β-CD: Meclizine HCl molar ratio of 1:1, in all system samples of the binary system (equivalent to about 50 mg of Meclizine HCl), were dissolved in the mobile phase (1-heptanesulfonic acid) which was diluted to obtain 0.1mg/ml. The HP-β-CD drug ratio would therefore remain 1:1 in the final solution to calculate the drug content. The drug content in all the system was found to be 99.42–102.36%.

In vitro dissolution studies

The release rate profile was drawn as the cumulative percent release on the *y*-axis and time on the *x*-axis shown in Figure 12. It showed that the inclusion complex of Meclizine HCl prepared by the kneading method released 79% drug in 10min, and up to 95% drug in 30min while the inclusion complex prepared by the co-precipitation method showed 73% drug release in 10min and up to 90% drug release in 30min. Physical mixtures show release up to 60% in 10 min and up to 80% drug release in 30min, whereas the pure drug exhibited the release of 25% in 10min and 55% drug release in 30min.[32] It was evident that the complex exhibited the faster dissolution rate than Meclizine HCl alone. The very high increase of Meclizine HCl dissolution rate in the case of inclusion complex might be due to several reasons. The formation of soluble inclusion complex, amorphization of

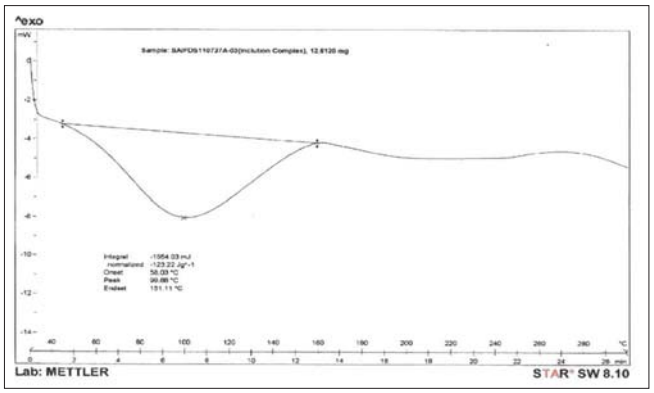

Figure 6: DSC thermogram of the kneading complex

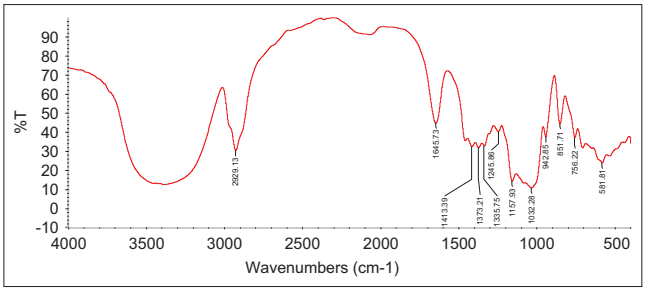

Figure 8: FT-IR spectra of HP-β-CD

drug and consequently solubility increase, better wettability and reduction of particle size.

Evaluation of precompression parameters of powder blend

The angle of repose of the powder blend was found to be 29.58°. The bulk density, tapped density, % compressibility and Hausner's ratio were found to be 0.625g/cm^3, 0.714g/cm^3, 12.46%, and 1.142%, respectively.

Evaluation of postcompression parameters of tablets

The hardness of the prepared tablet was found to be 3.3 ± 0.22kg/cm^2. Friability was found to be 0.51%, which were below 1% indicating sufficient mechanical integrity and strength of prepared tablets. The disintegration time was found to be 58.34 ± 0.57 s. Weight variation was found to be 200.21 ± 3.434mg which was within the permissible limit of ±7.5%. The *in vitro* dissolution studies showed that almost 69% of the drug was released within 10min and almost 96% of the drug was released at the end of 30min. The prepared tablets were compared with the marketed tablet, and the dissolution parameters of both formulations are shown in Table 2 and Figure 13. The drug content was found to be 98.54%.

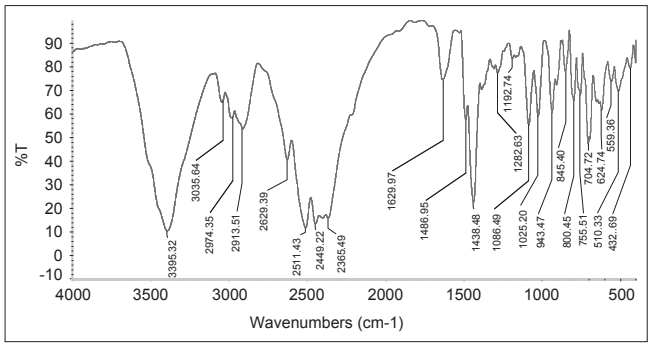

Figure 7: FT-IR spectra of Meclizine HCl

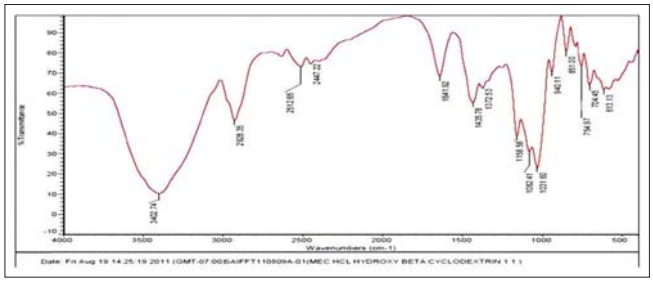

Figure 9: FT-IR spectra of physical mixture

Table 2: Comparison of dissolution data of prepared tablet and marketed tablet

Time (min)	% Release from prepared tablet[a]	% Release from marketed tablet[a]
5	44.44 ± 0.61	3.49 ± 0.32
10	68.28 ± 0.46	9.87 ± 0.23
15	72.34 ± 0.64	22.43 ± 0.93
20	78.31 ± 0.48	28.98 ± 0.34
25	84.12 ± 0.46	34.93 ± 0.94
30	95.16 ± 0.64	53.39 ± 0.45
45	-	70.39 ± 0.50
60	-	81.39 ± 0.49

[a]Mean ± SD, $n = 3$

DISCUSSION

From the result it is observed that the solubility of Meclizine HCl in the presence of β-cyclodextrin and HP-β-CD can be classified as the A_L type. This indicated that the complexes at 1:1 ratio are adequately stable and also the extent of solubility enhancement being higher for HP-β-CD. The DSC thermogram for the physical mixture showed the persistence of the endothermic peak of Meclizine HCl. Though there is reduction in peaks intensity, this can be explained on the basis of major interaction between the drug and HP-β-CD. Furthermore, the characteristic endothermic effect of HP-β-CD and Meclizine HCl is slightly shifted to lower temperature for the physical mixture indicating partial complexes formation, i.e. some parts of Meclizine HCl entrapped in HP-β-CD cavity. The enhancement in the dissolution profile has been attributed due to the formation of inclusion

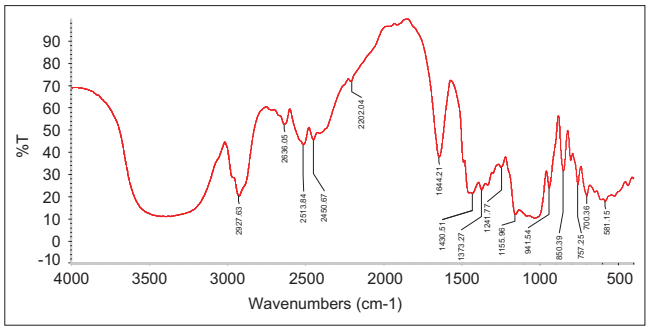

Figure 10: FT-IR spectra of the kneading method

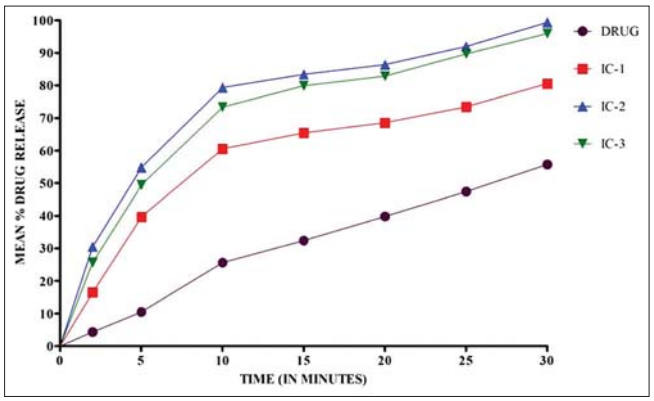

Figure 12: Dissolution rate profile of Meclizine HCl–HP-β-CD systems

complexes in the solid state and reduction in the crystallinity of the product. While the DSC thermogram of the kneading complex shows the complete disappearance of the Meclizine HCl endothermic peak and flattening of endotherm which indicates the formation of true complex and conversion of a drug-to-amorphous form, a small exothermic peak was obtained is due to the recrystallization of some drugs. The dissolution rate increase for the physical mixture, kneaded and co-precipitation mixtures is due to the wetting effect of the HP-β-CD, this effect is more evident for the kneaded product, where the mixing process between the two components is more intensive. The effect of complexation with HP-β-CD on the solubility of Meclizine HCl can be explained in terms of the reduction in the crystallinity of the drug and conversion to amorphous form by inclusion into the hydrophobic cavity of the HP-β-CD. The FTIR spectra of the physical mixture showed no significant alterations in the IR bands of the pure drug. However, some of the peaks of Meclizine HCl were slightly shifted and found to be attenuated. The broadening of peak was probably due to the restriction of bending and stretching vibration of the Meclizine HCl due to the HP-β-CD cavity. However, the IR spectrum of the physical mixture could be diagnosed as a superimposition of the bands of the pure drug. Significant changes were recorded in the IR spectrum of the inclusion complex. Almost all peaks of Meclizine HCl were smoothened indicating strong physical

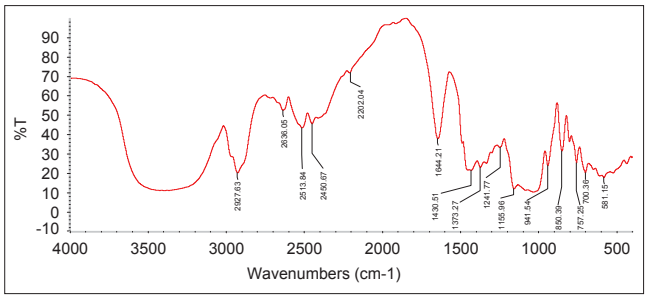

Figure 11: FT-IR spectra of co-precipitation

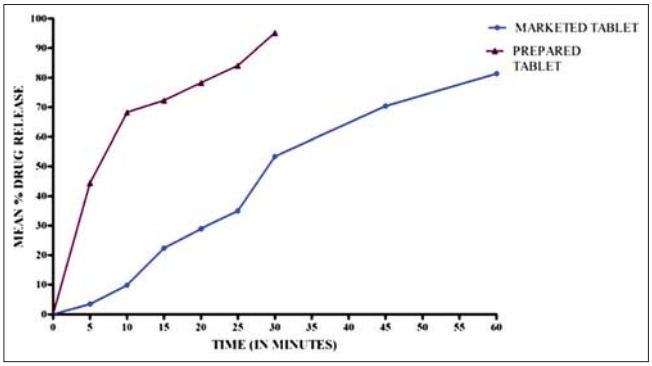

Figure 13: Comparison of dissolution profiles of the prepared tablet and marketed tablet

interaction between pure drug and HP-β-CD, indicating the formation of inclusion complex in the solid state. All the binary systems of Meclizine HCl-HP-β-CD did not show any new peaks, indicating noncovalent interaction in the inclusion complex. *In vitro* drug release from prepared tablets shows significantly improved drug dissolution as compared to the marketed tablet of Meclizine HCl. Hence, it could be concluded that the solubility enhancement of Meclizine HCl could be successfully achieved by the inclusion complexation technique and inclusion complex based fast dissolving tablets of Meclizine HCl would provide quick-onset of action.

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