RESEARCH ARTICLE

Long Term Stability and *In-vitro* Release Study of Telmisartan Complex included by Hydroxypropyl-beta-cyclodextrin in Directly Compressed Tablet Using Ion-pair Reversed Phase High-performance Liquid Chromatography

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ABSTRACT

Telmisartan is widely used angiotensin II type antihypertensive drug. It poses a poor solubility in water which leads to low bioavailability in blood stream so that; this problem guides many scientists to work for improvement of Telmisartan dissolution. The objective of this work is improving stability and dissolution of Telmisartan tablets using a safe and potential solubilizing agent (hydroxy propyl betacyclodextrin) in comparison to sodium hydroxide or Meglumine. Ten formulas were prepared using cyclodextrin (CD) at different ratios with formula contains sodium hydroxide and another contains Meglumine by direct compression method. The prepared formulas were evaluated for friability, hardness, drug content, disintegration, dissolution, FTIR, and DSC, in addition to short term and long shelf stability study for three years utilizing developed ion pair high-performance liquid chromatography (HPLC) technique. The results indicated as the ratio of cyclodextrin to drug increase the dissolution increased and best ratio is 3:1 and significantly ($p < 0.05$) higher than other ratios and formula used NaOH or Meglumine with confirmed stability for three years in addition to that fourier-transform infrared (FTIR) and differential scanning calorimeter (DSC) analysis indicate no chemical interaction was observed. It can be concluded that the prepared telmisartan tablet by simple direct method using safe inclusion complex is good candidate for easily prepared stable telmisartan tablet

Keywords: Inclusion cyclodextrin, Ion pair HPLC, Shelf Stability, Telmisartan.

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Conflict of interest: None

INTRODUCTION

Telmisartan is an angiotensin II receptor antagonist and used in the management of hypertension. It is practically insoluble in water and causes low percentage rate on dissolution. Telmisartan is absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% after a 40-mg dose.[1] Several scientists planned their works to establish a formulation of Telmisartan tablets with high dissolution which were performed by using an alkalizing agent as sodium hydroxide or using different hydrophilic polymers or surfactants. However, these formulated products may lack the stability of active substances on stressed conditions of storage.[2-4] Some other workers have applied agglomerated crystals technique for enhancing Telmisartan solubility; this technique is rather tedious and consumes organic solvents.[5] Other scientists used surface solid dispersion techniques to enhance the dissolution of Telmisartan tablets.[6] The naturally derived starch material, beta-cyclodextrin is produced, and its various derivatives have been widely applied nowadays in pharmaceutics to solubilize poor soluble drugs in dosage forms by inclusion complex with the drug.[7,8] Different methods have been used to prepare inclusion complexes of drugs with beta-cyclodextrins or its derivatives. These methods consist of mixture formation of the drug at different ratios with cyclodextrins by physical mixing or kneading method. Here, the mixture of the components is wetted with water or methanol to form a paste, then dried, sieved, and ground, or by co-precipitation method in which the drug is dissolved in polar organic solvent and mixed with cyclodextrins in water until a clear solution is obtained then the solvent is evaporated to give amorphous powder.[9]

In this work, the kneading method was selected for inclusion complex formation as it is rapid and proper. The work planned a three-year shelf stability study of the direct

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method of the simple telmisartan complex incorporated in tablets.

MATERIALS AND METHODS

Materials

Safa Company supplied telmisartan and hydroxyl propyl beta-cyclodextrin (HP-βCD) for pharmaceutical productions, Iraq. Meglumine and Croscarmellose sodium were obtained from Cadila healthcare ltd., Ahmedabad, India. For HPLC mobile phase; solvent with HPLC grade was used. For other reagents, reagent grade materials were used.

Methods

Telmisartan-HP-βCD Complex Preparation

Inclusion complex was prepared by kneading method at different ratios of drug: HP-βCD (1:1, 1:1.25, 1:1.5, 1:1.75, 1:2, 1:2.25, 1:2.5, 1:2.75, and 1:3. The Telmisartan and HP-βCD were previously sieved individually through sieve No.60 and weighed at specified weight ratios, mixed well in a mortar. A suitable amount of water was added with trituration until a smooth paste is formed. The trituration was continued for three hours and then dried the mass by hot air. The dried mass was ground to a fine powder.

The evidence of inclusion complex formation between HP-βCD and Telmisartan was identified by FTIR-scanning (Bruker Co., Germany), and the effect of the complex on the nature of Telmisartan was studied by DSC scanning (Shimadzu DSC60, Japan) of the powder mixture.

Manufacturing of Tablets

Formula F1 tablet was prepared using pure Telmisartan while formulas (F2–F10) tablets were prepared using Telmisartan-HP-βCD complex at different ratios as shown in Table 1. Formula F11 used NaOH, while formula F12 used Meglumine as a solubility modifier with pure Telmisartan. Direct compression technique was applied for tablets preparation by using ready Direct Compression Excipients (DC-excipients) made according to the previous procedure.[10]

HPLC Analysis

A specific and precise method was developed in this work for the quantitative determination of Telmisartan in tablet dosage form by using ion-pair reversed-phase HPLC, which approved its suitability for stability study since it showed good resolution between the Telmisartan and its degradation product, particularly the alkali degradation. This method of analysis consists of using a column C18; (4.6 × 150 mm) in diameter, mobile phase; 0.1M potassium phosphate with the addition of 0.05% n-heptane sulphonate sodium, the pH adjusted to (5.5), this buffer solution is mixed with Methanol (60:40), the detection by UV at 230 nm and the flow rate 1.5 mL/min. Validation. The efficiency of the developed HPLC method was validated for precision, accuracy, reproducibility, specificity, and this technique's ability to identify the degradation products.

Preparation of alkali degradation product: transfer 12.5 mL of the standard solution of Telmisartan as described in quantitative analysis to 50 mL volumetric flask, add 10 mL of 0.1N sodium hydroxide solution, stir for 30 minutes, then complete to volume with mobile phase solution, store for 24 hours at 50ºC, then analyzed by HPLC.

Evaluation of the Prepared Tablets

The manufactured Telmisartan tablets were evaluated for hardness, friability, disintegration, dissolution tests, and assay.

Drug Content of Prepared Tablets

The samples solutions of Telmisartan tablet is prepared by transferring the equivalent weight of 44 mg of Telmisartan from 10 tablets powder to 100 mL volumetric flask with the aid of 50 mL of Methanol, add 1-mL of 0.5 N sodium hydroxide solution, shake well and sonication until clear solution, complete the volume by Methanol, inject in the chromatogram

Table 1: Composition of the prepared formulations of Telmisartan tablets using different solubilizers

Formula	*Telmisartan (mg)*	*HP-BCD (mg)*	*Ratio drug:CD*	*NaOH (mg)*	*Meglumine (mg)*	*DC-excipient (mg)*	*Cross-caramellose (mg)*	*Magnesium stearate (mg)*	*Total weight (mg)*
F1	40	0	1:0.00	0	0	460	10	10	520
F2	40	40	1:1.00	0	0	420	10	10	520
F3	40	50	1:1.25	0	0	410	10	10	520
F4	40	60	1:1.50	0	0	400	10	10	520
F5	40	70	1:1.75	0	0	390	10	10	520
F6	40	80	1:2.00	0	0	380	10	10	520
F7	40	90	1:2.25	0	0	370	10	10	520
F8	40	100	1:2.50	0	0	360	10	10	520
F9	40	110	1:2.75	0	0	350	10	10	520
F10	40	120	1:3.00	0	0	340	10	10	520
F11	40	0	—	2	0	458	10	10	520
F12	40	0	—	0	25	435	10	10	520

and the resulted peak area is compared with that of standard solution prepared by the same procedure and concentration (0.11 mg/mL by dilution with mobile phase).

In-vitro Dissolution Study

Dissolution test has been carried for the tablets by application of USP36 procedure, using the apparatus of paddle system (75rpm), the medium consists of phosphate buffer pH (7.5), 900 mL, the running time of apparatus was 30 minutes and the dissolved amount of Telmisartan in medium was determined by HPLC method.

Stability Study

Samples of Telmisartan tablets prepared by inclusion complex with HP-βCD, manufactured by direct compression and packed in blister were stored at (40ºC & 75%RH) for 6 months. On other hand, other samples of Telmisartan tablets in their blister packing were stored for long term at (30ºC and 65% RH) for three years, according to WHO Stability Guideline.

RESULTS AND DISCUSSION

Validation of Analytical Method

The used ion-pair reversed-phase HPLC method was applied and approved its efficiency since the calculated number of plates for the used column in analysis of Telmisartan was about 3500 and the other validation parameters were examined.

Precision: Different dilutions of Telmisartan in the range between 4–20 mg per 100 mL solution were prepared and analyzed by this method, a straight line was established according to the peaks areas responses (calibration curve) as shown in Figures 1.

- **Accuracy**: Samples of Telmisartan tablets of different strengths; 20, 40, and 80 mg Telmisartan per tablet were prepared accurately and then subjected to the assay procedure by HPLC. The results were 100.1, 99.8 and 100.5%, respectively, which indicated the accuracy of the HPLC method for Quantitative analysis.
- **Reproducibility**: Sample of Telmisartan solution of a definite concentration was analyzed by injection of several times and the resulted peak areas were recorded as following; 6.45, 6.51, 6.43, 6.40, 6.44 and the calculated RSD% was (0.625%). Note: for the efficient analytical method, the USP limit of RSD% should be not more than 2%.
- **Specificity**: the developed HPLC method showed a specific peak of Telmisartan with a retention time about (7.4 minutes). The chromatogram of separation did not show any interference from the excipients of the tablet with the peak of interest, see Figure 2.
- **Degradation:** Analysis of the deliberately degraded solution of Telmisartan showed good resolution between the peak of degradation product and that of Telmisartan, see Figures 3.

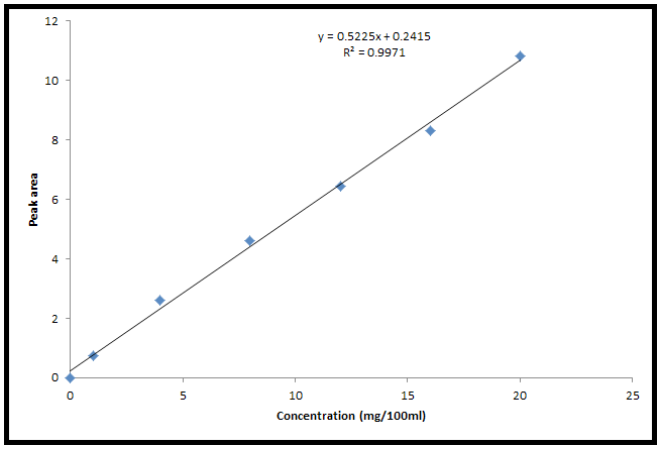

Figure 1: HPLC calibration curve of Telmisartan using peak areas versus concentrations.

Characterization Results of Telmisartan-HP-βCD Complex

The FTIR-scanning of Telmisartan complex with HP-βCD showed overlapping of HP-βCD spectra characterized by a wide band between 3300–3500 cm^{-1} due to O-H stretching vibration, and the (-CH) and (-CH2) vibration between 2800–3000 cm^{-1} region. The characteristic peak of Telmisartan at 1693 cm^{-1} for (-COOH) was disappeared in the complex spectra and also the absence of the peak at 757 cm^{-1} of ring vibration. These changes in FTIR-spectra of the mixture indicating formation of inclusion complex of Telmisartan in HP-βCD molecule see Figures 1, 2, and 3 for Telmisartan, HP-βCD, and their inclusion complex, respectively.

The differential scanning calorimeter analysis of Telmisartan inclusion complex showed no change in the endothermic peak from that of Telmisartan alone, and still, the melting point is about 261ºC, see Figures 7 and 8. These results indicated that the nature of Telmisartan did not influence by its inclusion complex with HP-βCD.

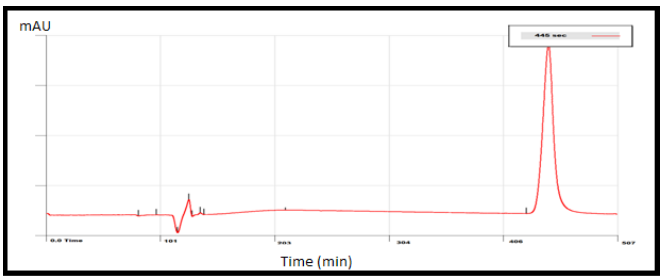

Figure 2: HPLC chromatogram of Telmisartan from selected formula tablet (F10)

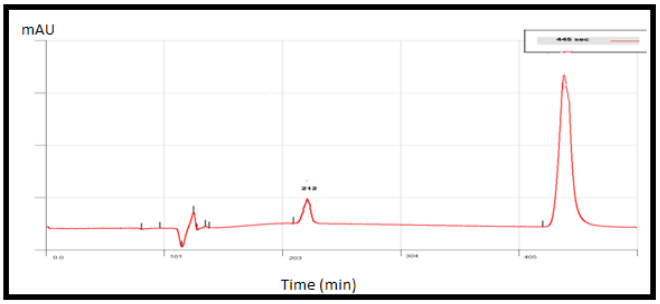

Figure 3: HPLC chromatogram of degraded solution of Telmisartan

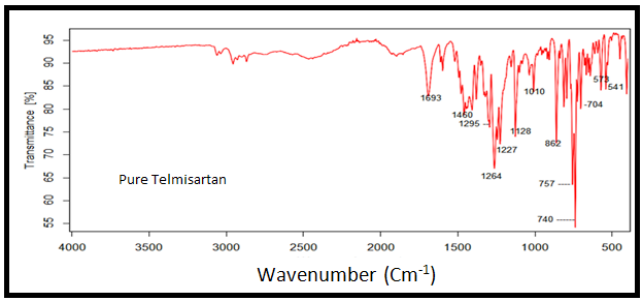

Figure 4: FTIR-spectrum of pure Telmisartan

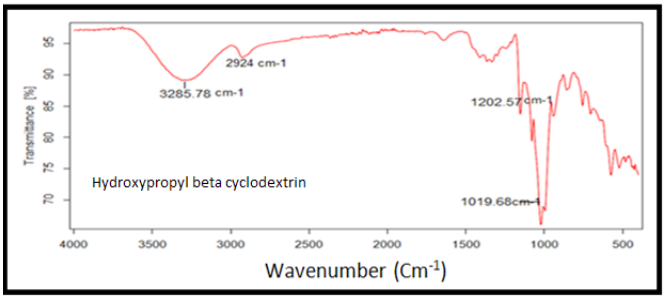

Figure 5: FTIR-spectrum of hydroxypropyl-beta-cyclodextrin

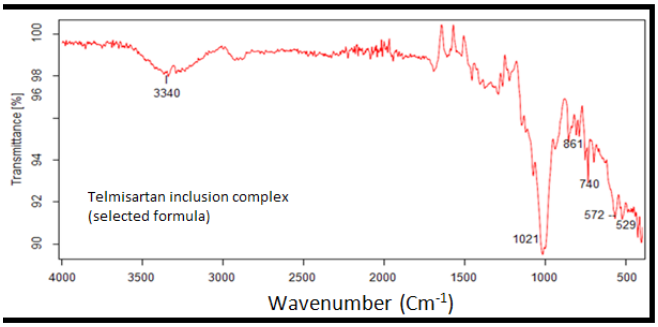

Figure 6: FTIR-spectrum of Telmisartan inclusion complex with HP-βCD (1:3)

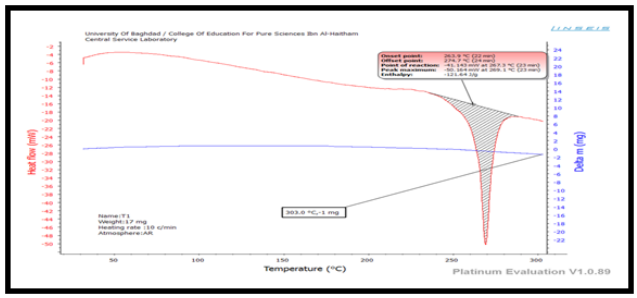

Figure 7: DSC thermograph of pure Telmisartan

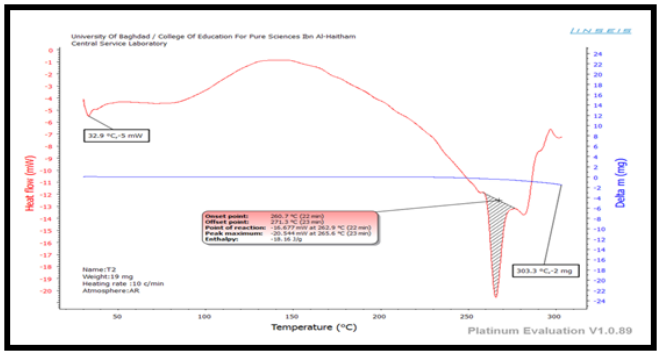

Figure 8: DSC thermograph of Telmisartan inclusion complex with HP-βCD (1:3)

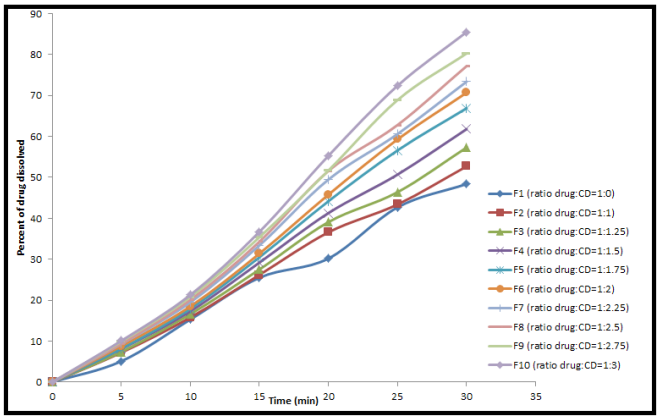

Figure 9: Comparison of dissolution profiles of Telmisartan from inclusion complex at different ratios in tablet and pure Telmisartan tablet

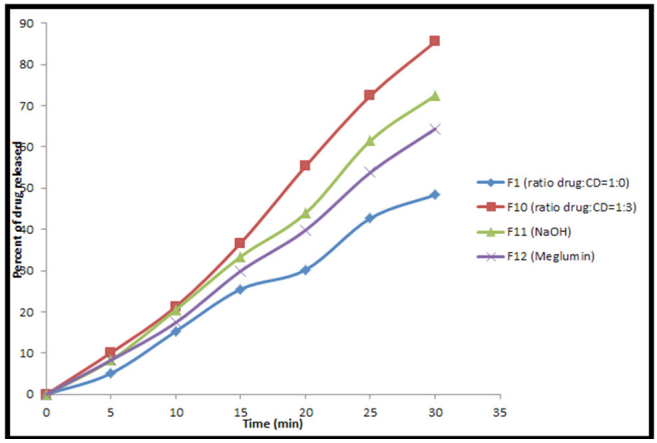

Figure 10: Comparison of dissolution profiles of Telmisartan tablet using CD, NaOH, meglumine, and pure telmisartan

Table 2: The evaluation data of prepared Telmisartan tablets

Formula number	*Hardness Kg/Cm²*	*Friability %*	*Disintegration Time (min)*	*Dissolution percent at 30 min*	*Assay %*
F1	6	0.45	2.5	48.4	99.6
F10	6.5	0.5	3	85.5	100.1
F11	6.8	0.7	5	75.5	100.3
F12	6.5	0.6	5	64.4	99.9

Table 3: Accelerated stability data of prepared selected formula of Telmisartan tablet (F10)

Test	*Initial time*	*1st month*	*2nd month*	*4th month*	*6th month*
Appearance	White & smooth	No change	No change	No change	No change
Hardness (Kg/cm²)	6.5	6.6	6.8	6.7	6.8
Friability (%)	0.5	0.56	0.56	0.56	0.58
Disintegration time (min)	3	3.5	3.5	3.7	3.8
Dissolution percent at 30 min	85	87	87	86	86
Assay (%)	100.1	99.8	99.7	99.8	99.8
Degradation signs	Non	Non	Non	Non	Non

Table 4: The stability data of prepared selected formula of Telmisartan tablet (F10) stored at 30ºC & 65% RH for 3 years.

Test	*Initial*	*1st month*	*3rd month*	*6th month*	*1st year*	*2nd year*	*3rd year*
Appearance	White &smooth	No change	No change	No change	No change	No change	No change
Hardness (kg/Cm^2)	6.5	6.5	6.8	6.7	6.8	7.1	7.0
Friability (%)	0.5	0.51	0.55	0.56	0.58	0.61	0.60
Disintegration time (min).	3	3.2	3.4	3.4	3.7	3.6	3.6
Dissolution percent at 30 min	85.5	84	85	85	86	84	84
Assay (%)	100.1	100	99.8	100	99.8	99.7	99.5
Degradation sign	Non	Non	Non	Non	Non	Non	

Evaluation of the Prepared Tablets

The pharmaceutical tests on manufactured Telmisartan tablets of formula F1 that use pure Telmisartan, selected formula (F10) of Telmisartan inclusion complex with HP-βCD (1:3), Formula use NaOH (F11), and formula use meglumine (F12) were listed in Table 2.

Dissolution Study

The dissolution of Telmisartan from the inclusion complex at different ratios as shown in Figure 9 indicate that as the ratio of drug to cyclodextrin increased, the dissolution enhanced significantly ($p < 0.05$) utilizing formula F2–F10 in comparison to formula use pure Telmisartan (F1).

On the other hand, the best formula of inclusion complex (Formula F10) in comparison to formula use NaOH (F11) as a solubilizing agent and formula use meglumine as solubilizing agent shows that formula F10 the highest dissolution than other although using simple safe, natural cyclodextrin in addition to low cost making this formula the optimum selected formula.

Stability Study

The physical and chemical properties of samples of the prepared selected formula of Telmisartan tablets (F10) stored at accelerated conditions for 6 months are shown in Table 3 and at long-term storage for three years, Table 4. The results demonstrate that the percentages and the physical characters of Telmisartan tablets stored did not show any significant changes.

CONCLUSION

This work indicated that using inclusion complex formation of Telmisartan with HP-βCD carry the drug in aqueous vehicle and enhances the dissolution rate. On the other hand, the HP-βCD of polysaccharide structure holds the drug within its cavity in solid-state without chemical interaction and protects the inclusion drug complex from environmental challengers' impacts, hence improving drug stability.

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