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RESEARCH ARTICLE

Dissolution Enhancement of Clarithromycin Using Ternary Cyclodextrin Complexation

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ABSTRACT

The research work presented is new and never been done earlier. Clarithromycin, a semi-synthetic macrolide antibiotic derived from erythromycin having low solubility and high permeability falling in class-II of Biopharmaceutical Classification System (BCS). The drug is practically insoluble in water exhibiting dissolution rate limited absorption. The objective of the research work increasing in the solubility, release properties of Clarithromycin and improve the bioavailability of Clarithromycin using ternary inclusion complex with Beta Cyclodextrin. The research work includes developing a multi-component system comprising of macrolide: Clarithromycin, Beta-cyclodextrin and a polymer Soluplus to attain enhanced solubility of Clarithromycin. The inclusion complexes were prepared by slurry evaporation and kneading method using different proportions of B-CD'S and Soluplus. The complexes were characterized by solubility, drug content uniformity, dissolution rate, similarity factor analysis and by HPLC. The ternary inclusion complexes prepared by the kneading method were evaluated for solubility enhancement and improved dissolution rate. Formulations with a Soluplus concentration of 20% w/w of drug content and solvent ratio of 70:30 (water: ethanol) showed more than 80% of drug release at the end of one hour.

KEYWORDS

Clarithromycin (CLM), Beta Cyclodextrin (BCD), Soluplus (SOL), Slurry Evaporation (SE), Kneading method (KN), HPLC

INTRODUCTION

Oral Drug delivery is the simplest and easiest way of administering drugs because of greater stability, smaller bulk, and easy production. Clarithromycin (CLM), a broad-spectrum macrolide, is a poorly soluble drug with dissolution rate limited absorption. The low aqueous solubility (<0.1mg/ml in water at 298^{o}k) and slow dissolution may lead to irreproducible clinical response or therapeutic failure[1]. Thus it's important to have effective methods to enhance the solubility and dissolution rate of the drug. There are many ways of improving bioavailability one of which is complexation with hydrophilic carriers.[2,3]

The main perspective of the present study aims to attain maximum solubility enhancement for Clarithromycin using ternary cyclodextrin complexation. The multi-component system derived consists of Clarithromycin (CLM), Beta – Cyclodextrin (BCD) and Soluplus (SOL). Evaluation of ternary inclusion complexes was done using the accurate analytical technique of High-Performance Liquid Chromatography

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(HPLC). HPLC analysis of Clarithromycin was performed on Shimadzu LC-2010CHT as per method described in USP-13 edition. It has a serial dual plunger with a microvolume of 10 µl on the primary side and 5 µl on secondary. The HPLC conditions were as follows: 4.6-mm x 150- mmC-18 column, mobile phase consisted of degassed and pre-filtered Solvent A (0.067M monobasic potassium phosphate): Solvent B (Methanol) in a ratio of 65 : 35, adjusted with phosphoric acid to a pH of 4.0 pumped at a flow rate of 1 ml/min. Injection volume was kept at 50 µl. The UV detector was set at 210nm. Quantification was based on the peak area measurement.

The concentration of standard stock solution 625 µg/mL of Clarithromycin was prepared by dissolving Clarithromycin in methanol. A Standard solution of 125 µg/mL of Clarithromycin solution was prepared from the Standard stock solution by diluting with mobile phase and analyzed at 210nm for obtaining the standard peak area.

When a water-soluble polymer, a CD, and a Drug are mixed together in a solution, the increase in drug solubilization is a result of a synergistic effect between these components. In the presence of water, the polymer aids in the wettability of particles, resulting in an increased dissolution and increased amount of drug invitro.

The bioavailability of a drug in a formulation containing aqueous CD solutions depends on the ability of the drug molecules to interact with CD molecules and the Drug:CD concentration ratio[4,5]. Because the drug–CD interaction is affected by other excipients present in the drug formulation, it is of the utmost importance to optimize the final drug formulation with regard to the amount of CD[6].

Soluplus is a polymeric solubilizer with an amphiphilic chemical nature, which is particularly developed for solid solutions. Soluplus is polyvinyl caprolactam– polyvinyl acetate – polyethylene glycol graft copolymer. It increases the solubility and enhances the bioavailability of actives.

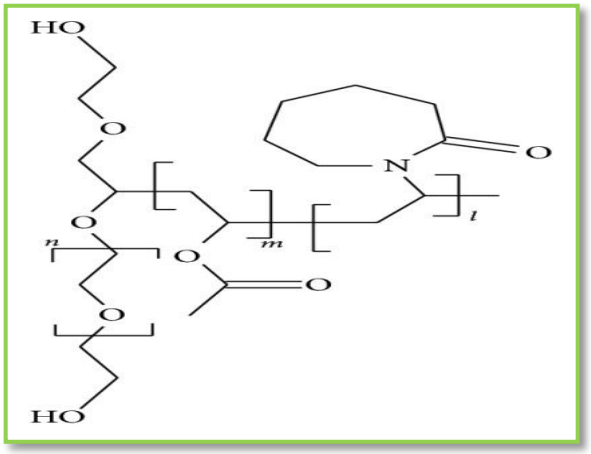

Figure : 1

MATERIALS AND METHOD

Clarithromycin and Soluplus were procured as a gift sample from Naprod life sciences and BASF respectively. BCD was procured as a gift sample from Signet. HPLC analysis was performed at Naprod Life Sciences under the supervision of Research analyst on Schimadzu LC-2010CHT. Other chemicals used were of analytical grade.

Docking Studies

Docking studies were done in order to study the binding energy of Clarithromycin to cyclodextrin. Studies were conducted using Auto dock Vina 1.1.2. Beta-cyclodextrin acted as a receptor and Clarithromycin as a ligand. Flexible docking of (CLM) Clarithromycin superimposed on the crystal structures of (CD) beta cyclodextrin[7].

The data is shown in table 4 and fig. no 2 and 3.

Phase Solubility Studies

Phase solubility studies for ternary inclusion complexes in water were carried out according to Higuchi and Connors method (Higuchi and Connors, 1965).

An excess amount of Clarithromycin (50mg) was added to 10 ml aqueous solution of a different molar concentration of β-CD (6mM and14mM) with HPLC grade water.

A series of solutions were prepared for the polymer, in the range of 4 to 80 % w/w of the drug. Studies were conducted to evaluate the

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influence of the different concentration of polymer on the complexation efficiency of B-CD. Two sets of 10 ml were prepared as follows. The flasks were placed on a mechanical shaker for 48 hr. at room temperature (30 ± 2ºC). Suitable aliquots were filtered through Whatman filter and analyzed by HPLC at 210nm.

Table : 1

Sr. No.	BCD molar Conc x 10^{-1}	Amount of Soluplus In % w/w of CLM
Ref	0.06M	0
Ref	0	10
Set I	0.06M	4
Set I	0.06M	10
Set I	0.06M	20
Set I	0.06M	80
Set II	0.14M	4
Set II	0.14M	10
Set II	0.14M	20
Set II	0.14M	80

A known excess of CLM (50mg) was added and all the flasks were kept on a mechanical shaker at 30 ± 2°C for 48 hr.

The apparent solubility constant (KS) and complexation efficiency (CE) was calculated as follows[8,9]:

$$KS = Slope / S_o (1 – Slope)$$

Complexation efficiency (CE) = Slope / (1 – Slope)

Where, S_o is the solubility of the drug in absence of β-CD.

Method of preparation of Ternary Inclusion Complexes[10,11,12]

Slurry Evaporation Method (SE)

The required amount of CLM, β-CD, and SOL were taken in a mortar to which solvent has added a mixture of water-ethanol in the ratio of 50:50 to form a slurry. The resulting powders were dried at room temperature, sieved through a mesh number (80#) and stored in a desiccator for subsequent use.

Kneading method (KN)[13,14]

The required amount of CLM, β-CD, and SOL were taken in a mortar to which the solvent for kneading was added just sufficient to form a paste. A solvent mixture of water-ethanol in the ratios 50:50, 60:40 and 70:30 was used. Obtained powders dried at room temperature, sieved through the mesh (80#) and stored in a desiccator for subsequent use.

Prepared batches

Table 2: Slurry evaporation

Run	Drug:BCD	Soluplus (% w/w of drug)	Water: Ethanol ratio
1	1:1	4	50:50
2	1:1	10	50:50
3	1:1	20	50:50
4	1:2	4	50:50
5	1:2	10	50:50
6	1:2	20	50:50

Table 3: Kneading technique

Run	Batch no	Drug:BCD	Soluplus (% w/w of drug)	Water: Ethanol ratio
1	F1	1:2	4	50:50
2	F2	1:2	10	50:50

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3	F3	1:2	20	50:50
4	F4	1:2	4	60:40
5	F5	1:2	10	60:40
6	F6	1:2	20	60:40
7	F7	1:2	4	70:30
8	F8	1:2	10	70:30
9	F9	1:2	20	70:30
	B-7	1:1	0	50:50

Evaluation of Prepared Ternary Inclusion Complexes

Docking Studies

Studies were conducted using Auto dock Vina 1.1.2. Beta-cyclodextrin acted as a receptor and Clarithromycin as a ligand. Flexible docking of (CLM) Clarithromycin superimposed on the crystal structures of (CD) beta-cyclodextrin.

Table 4: Tabular representation of the data obtained through the docking

Mode	Affinity (kcal/mol)	rmsd l.b	rmsd u.b.
1	-4.9	0.000	0.000
2	-4.8	2.267	7.638
3	-4.8	2.351	7.507
4	-4.7	1.232	2.045
5	-4.6	1.182	1.286
6	-4.4	2.234	4.953
7	-4.4	2.196	5.056
8	-4.3	1.987	7.507
9	-4.3	1.883	5.218

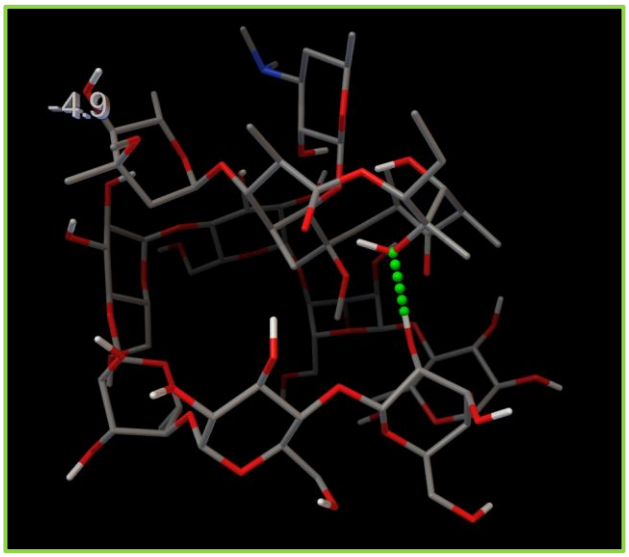

Figure : 2

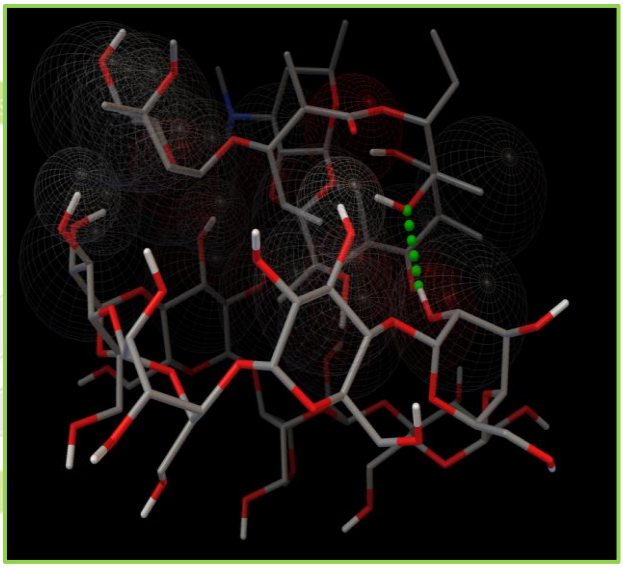

Figure : 3

Docking studies of Clarithromycin confirmed the possible host-guest inclusion complex formation. The minimum binding energy observed was -4.9 kcal/mol. Interaction responsible were H-bonding and Van der Waals forces[15].

For the binding of Clarithromycin with CD having a binding energy of -4.9 kcal/mole, Clarithromycin forms Hydrogen bonds with the H122 hydrogen atom of the beta-cyclodextrin, H of cyclodextrin acts as a receptor.

Docking studies indicated the insertion of Clarithromycin into the Beta- Cyclodextrin cavity suggesting the co-existence of

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Clarithromycin and Beta- Cyclodextrin complexes in equilibrium with each other.

Solubility Studies

A predetermined amount of ternary inclusion complexes equivalent to 12.5mg Clarithromycin were weighed and analyzed for drug dissolved in water at the end of 30 mins.

Table 5: Batch Details

Sr. No.	Batch Details (Sol in %)	Method of preparation	Time Span	Peak area
1	1:1:4	SE	45 min	141992
2	1:1:10	SE	45 min	167174
3	1:1:10	KN	45 min	181323
4	1:2:10	KN	30 min	267456
5	1:1:20	KN	45 min	297456

In- vitro Dissolution

The in-vitro dissolution test for Clarithromycin pure drug and ternary inclusion complex were carried out in a USP Type II apparatus using dissolution medium (Acetate buffer pH 5.0), of 900ml at 50rpm. The temperature of the medium was maintained at 37+-0.5˚C. 5ml of the sample was withdrawn at a predetermined time interval of 5, 10, 30, 45, 60, 90, 120 min and replaced with fresh dissolution medium. The sample solution was diluted with the dissolution medium and analyzed by HPLC. The HPLC conditions were as follows: 4.6-mm x 150- mmC-18 column, mobile phase consisted of degassed and pre-filtered Solvent A (0.067M monobasic potassium phosphate): Solvent B (Methanol) in a ratio of 65:35, adjusted with phosphoric acid to a pH of 4.0 pumped at a flow rate of 1 ml/min. Injection volume was kept at 50 µl. The UV detector was set at 210nm. Quantification was based on the peak area measurement.

Drug Content Estimation

Assay Procedure

Standard Solution: Clarithromycin 62.5 mg was dissolved in HPLC grade methanol to attain standard stock solution concentration of 625 µg/mL. A Standard solution of 125 µg/mL of Clarithromycin solution was prepared from the Standard stock solution by diluting with mobile phase and analyzed at 210nm for obtaining the standard peak area[16,17].

Sample Solution: The sample solution was prepared by weighing inclusion complexes equivalent to 62.5 mg of Clarithromycin and then was further treated as per assay procedure to obtain a concentration of 125 µg/mL theoretically.

Drug-Polymer Interaction Study

Differential Scanning Calorimetry (DSC)

Clarithromycin, Beta- Cyclodextrin, Soluplus, and ternary inclusion complexes were analyzed by DSC. Around 10mg of the sample was heated in an alumina pan at a temperature range of 30ºC – 300ºC at a rate of 10º C/min under nitrogen atmosphere. DSC thermograms of batches are shown in figure 6a to 6e.

RESULTS AND DISCUSSION

Phase Solubility Study

Table 6: Phase solubility results

Sr. No.	BCD molar Conc	BCD in mg	Amount of Soluplus (mg)	Peak area
Ref.	0.006M	68mg	0	412300
Ref	0	0	10	254275
Set I	0.006M	68mg	4	375565

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Set I	0.006M	68mg	10	421346
Set I	0.006M	68mg	20	427865
Set I	0.006M	68mg	80	203235
Set II	0.014M	158.3mg	4	417146
Set II	0.014M	158.3mg	10	480849
Set II	0.014M	158.3mg	20	578663
Set II	0.014M	158.3mg	80	305022

Table 7: Phase solubility data in terms of molar ratio

BCD moles	Amt. Of Sol % w/w of CLM	Peak area	Solubility	Solubility in molar concentration
0	10	254275	106.9 µg/ml	1.2×10^{-3}
0.014M	4	417146	175.3 µg/ml	2.1×10^{-3}
0.014M	10	480849	202 µg/ml	$2.42x\ 10^{-3}$
0.014M	20	578663	243 µg/ml	2.9×10^{-3}
0.014M	40	305022	128 µg/ml	1.5×10^{-3}

So = 0.49×10^{-3} moles/ml

Slope = 0.45

Ks= 1702

Complexation Efficiency = 0.88

% CE= 88%

The complex exhibits higher solubility than the guest molecule, but its limit is reached within the tested SOL concentration range. Increasing the amount SOL does not lead to a rise in solubility, indicating that all guest molecules have been converted into a more soluble inclusion complex, which denotes an initial rise in the solubility of the complex followed by a plateau.

The Clarithromycin solubility was improved nearly 6.2 folds as compared to the plain drug in aqueous 14mM B-CD solution with 20% Soluplus concentration. The marked increase in solubility of the hydrophobic drug can be explained by the mutual interaction among the components. Maximum peak area was obtained for 1:2:20 Drug:BCD:SOL which indicated the optimum ratio for ternary inclusion complex.

Assay Results

Drug content estimation

The percentage drug content of Clarithromycin from different formulae of ternary inclusion complexes

*Average peak area 311630

Table : 8

Batch	Expected content of Clarithromycin (mg)	Peak area	Observed content (mg)	% Drug content
F1	12.5	309230	12.40	99.23 ±0.12%
F2	12.5	308981	12.38	99.15 ± 0.17%
F3	12.5	309916	12.43	99.45 ± 0.23%
F4	12.5	307485	12.33	98.67 ± 0.15%
F5	12.5	311629	12.5	100 ± 0.1%

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F6	12.5	307236	12.32	98.59 ± 0.13%
F7	12.5	309697	12.42	99.38 ± 0.21%
F8	12.5	309947	12.43	99.46 ± 0.13%
F9	12.5	311632	12.5	99.32 ± 0.11%

***In- vitro* Dissolution Studies**

Dissolution profile observed for pH 6.8 in order to understand the enhancement in solubility due to complexation

Dissolution profile observed for pH 6.8 in order to understand the enhancement in solubility due to complexation

Table : 9

Time points	% CR F1	% CR F2	% CR F3	% CR F4	% CR F5
5	3.2	7	11	8.3	9.03
10	7.7	18	42	12.7	21.22
30	54.31	59.36	63	59.23	62.71
60	66.17	80.3	85.2	77.8	80.76
90	75.4	85.36	92	79.23	86.67
120	81.5	88	94	84	89.52

Time points	% CR F6	% CR F7	% CR F8	% CR F9
5	4.03	11.09	13.5	3
10	12.86	22.5	36.21	12
30	68.57	60.82	65.3	58
60	86.19	79.64	80.86	87.27
90	89.17	83.02	88.02	95.03
120	95.07	90	93	98

Comparison of dissolution profile of ternary inclusion complex with binary inclusion complex and pure drug

Table 10: % Cumulative release of Clarithromycin in Phosphate buffer pH 6.8

Time (mins)	Plain drug	B-7	F-±9
5	1.6 ± 0.12%	8 ± 0.06	3 ± 0.23
10	3.22 ± 0.12	37 ± 0.24	12 ± 0.17
30	15 ± 0.23	70 ± 0.19	58 ± 0.26
60	31 ± 0.14	82 ± 0.17	87.27 ± 0.17
90	39 ±0.23	88 ± 0.17	95.03± 0.18
120	49 ± 0.4	89 ± 0.21	98± 0.19

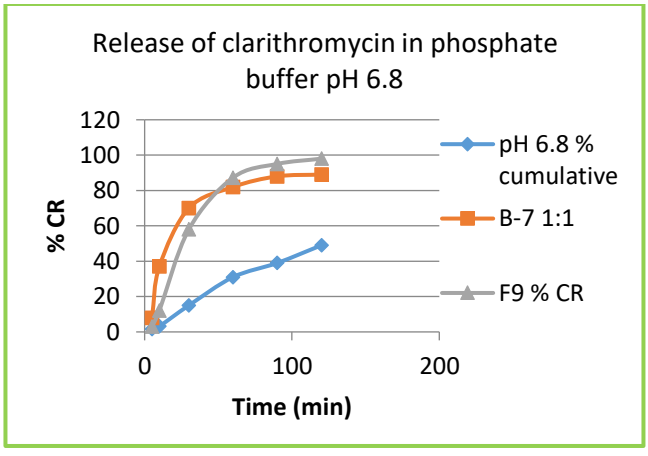

Figure : 4

Maximum % CR was observed for batch F9. Batches showed increased dissolution efficiency of Clarithromycin present in the formulations when compared to its pure form.

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Batch B-7 from the binary complexes and F-9 ternary inclusion complex have shown maximum solubility enhancement.

All the batches prepared above were evaluated for % drug content which was observed to be in the range of 98-100%.

It was observed that dissolution efficiency of Clarithromycin increases with increase in the concentration of Soluplus. The soluplus concentration of 20 % w/w of drug content showed maximum % CR. The solvent ratio of 50:50 (water: ethanol) showed comparatively less release even when the Soluplus concentration was 20%. It was observed that there was a considerable increase in % CR when the water content in the solvent ratio was increased.

Characterization of pure CLM, BCD, SOL and ternary inclusion complexes.

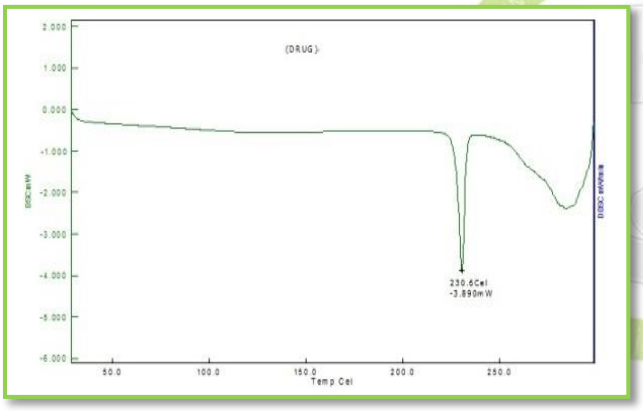

Figure 5a.: DSC thermogram for pure CLM

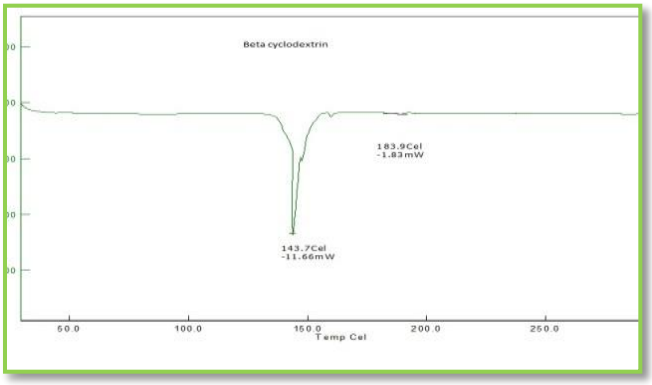

Figure 5b.: DSC thermogram of BCD

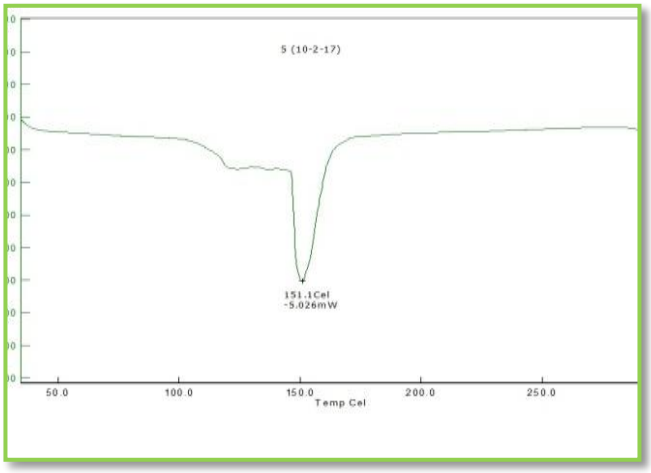

Figure 5c.: DSC thermogram of Soluplus

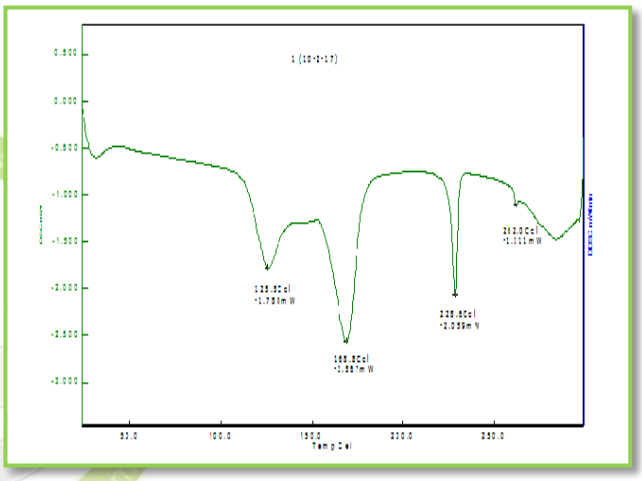

Figure 5d.: DSC thermogram of ternary inclusion complexes of 1:1:10 by slurry evaporation for 45 mins.

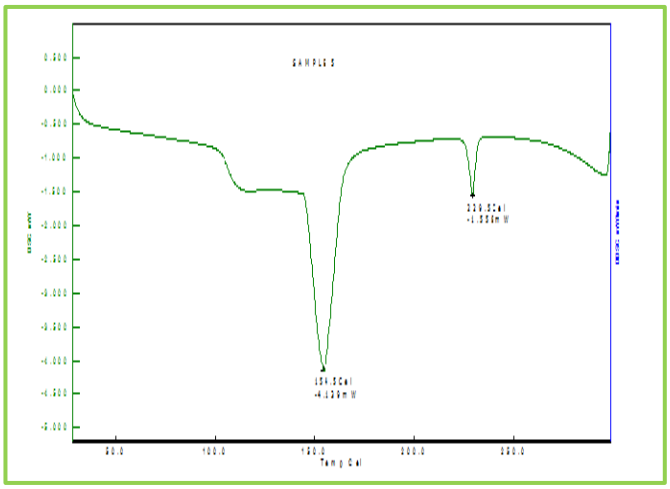

Figure 5e.: DSC thermogram of ternary inclusion complex of 1:2:10 by Kneading method for 45 min.

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The thermal curve of pure CLM was typical of a crystalline anhydrous substance with a sharp endothermic peak at 230.6°C corresponding to the melting point of the drug. Characteristic peaks of CLM and BCD were clearly distinguishable in ternary inclusion complexes prepared by slurry evaporation (SE) method. There was a substantial reduction in the Clarithromycin peak intensity for inclusion complexes prepared by kneading (KN) method in comparison to complexes prepared by SE method. The disappearance of the CLM endothermic peak in ternary inclusion complex 1:2:20 prepared by kneading KN method using 50:50 (water:ethanol) mixture for 45 min indicated the formation of amorphous entities and/or inclusion complexes. The results indicated that only the kneading (KN) products can be considered as true inclusion complexes, differing from slurry evaporation techniques used[18].

Comparison of dissolution profiles for ternary batches prepared with kneading technique.

CONCLUSION

For the quantification of Clarithromycin, High-Performance Liquid Chromatography (HPLC) method was used. Phase solubility studies were carried out to determine the stoichiometric ratio of Clarithromycin, BCD and in addition optimize the concentration of hydrophilic polymer SOL for ternary inclusion complex. Inclusion complex was prepared by slurry evaporation and kneading technique. The complexes were evaluated for drug content, solubility enhancement, and dissolution studies. The plain drug and complexes were also characterized by differential scanning calorimetry. Clarithromycin solubility in water is low. Phase solubility studies of Clarithromycin confirmed the solubility enhancement capabilities of cyclodextrins. The phase solubility curves indicated the formation of 1:2:20 (SOL % w/w of the drug) for ternary inclusion complexes. The phase solubility studies indicated that the aqueous solubility of Clarithromycin was greatly enhanced in presence of BCD and hydrophilic polymer SOL.

Clarithromycin alone and inclusion complexes prepared by physical mixing and slurry evaporation showed lower enhancement in solubility as compared to inclusion complexes prepared by kneading method. The solubility enhancement was found to be 6.4 folds for ternary complexes as compared to the plain drug. The % cumulative release was found to be 48% for Clarithromycin, and 98% for ternary inclusion complex respectively prepared by kneading technique.

Thus faster-acting capsules of Clarithromycin with better bioavailability could be successfully developed by employing BCD and SOL as a solubility and dissolution enhancer. This study further opens the chance of studying many other poorly water-soluble drugs, using the concept of ternary cyclodextrin complexation if the chemical stability of the drug remains unaffected and if the drug is compatible with the carrier used in this strategy.

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