Enhancement of Solubility of poorly water soluble drugs by using Complexol: A cyclodextrin based Approach

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***Abstract*:**
Objectives: The Aim of this Study was to develop and evaluate tablets using various concentrations of Complexol by Direct Compression Technique, which offers the enhanced Solubility and Dissolution Rate of poorly soluble drugs.
Methods: A Drug Telmisartan Hydrochloride, was selected for the Study. Different Formulations were prepared by Using Various Concentrations of Complexol B and Complexol HP. The Formulations were Prepared by Co Evaporation and Kneading Method. The Inclusion Complexes were then Compressed into Tablets.
Results: The physical and chemical properties of the complexes were characterized using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). The tablets were evaluated for various parameters including hardness, friability, drug content, and in vitro drug release, Solid State Characterization (FTIR, DSC, SEM and XRD). The Solubility of TLM in water was significantly Increased in an Average of 2 and 9-Fold by using Complexol B and Complexol HP resp. Results indicated that the drug shows better solubility with Complexol.
Conclusions: The Study Concluded that Inclusion Complexes of Telmisartan with Complexol B and Complexol HP have been Successfully Prepared. The Results of this study Highlight Complexol HP gave better Solubilization Effect for Insoluble Molecules.
Keywords: Cyclodextrins, Solubility, Inclusion Complex.

Introduction:
The oral route is the most common and preferred method of drug administration because of its convenience and ease of delivery as well as cost-effectiveness and better patient compliance. However, for many active pharmaceutical ingredients (APIs), this route of administration is associated with some drawbacks such as poor aqueous solubility and low permeability of the compound resulting in limited drug absorption and consequent poor bioavailability. For any drug to be absorbed, it must be available in an aqueous solution at the site of absorption. It is known that for drugs with solubilities < 0.1 mg/ml, their absorption is likely to be dissolution limited. Conversely, if a drug is extremely water soluble, its ability to traverse lipophilic bio membranes(permeability) will be poor and this also limits the bioavailability.
The critical impacts of aqueous solubility and intestinal permeability of drugs on their bioavailability have been utilized in classifying APIs into four classes, as reflected in the Biopharmaceutics Classification Systems (BCS). These two factors along with dissolution process, govern the rate and extent to which a drug appears in the systemic circulation, and this depicts bioavailability. For the BCS class II drugs (low aqueous solubility/high permeability) the rate-limiting step in drug absorption is the dissolution process. While for the BCS Class IV drugs (low aqueous solubility/low permeability), both dissolution process and intestinal permeability determine the drug absorption.
Thus, increasing the aqueous solubility can translate to increase in the dissolution rate with a resultant improvement in the oral bioavailability of BCS Classes II [1].

Drug absorption, bioavailability, pharmacokinetics profile of orally administered drug substances is highly dependent on the solubility of that compound in the aqueous medium. Solubility is the maximum amount of solute which can dissolve in a certain amount of solvent under standard conditions of temperature, pressure and pH. It is an important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The poor bioavailability of a drug is mainly concerned with its poor water solubility. Low water Solubility is the major problem encountered with the formulation development of new chemical entities. Therapeutic effectiveness of a drug depends upon the bioavailability. The process of solubilization involves the breaking of intermolecular or inter ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and solute molecule or ion [2].
Various techniques are used for the enhancement of solubility of poorly soluble drugs including physical and chemical modifications of drug like particle size reduction, crystal Engineering, salt formation, solid dispersion, use of Surfactant, Hydrotropy, cosolvency, use of surfactants and complexation. [3]
Complexation: Inclusion complex formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or host molecules. This technique has been most frequently employed to improve the aqueous

solubility dissolution rate and bioavailability of poorly water-soluble drugs. The most commonly used host molecules are Complexol [3].

COMPLEXOL:

The trade /chemical name of Complexol is Cyclodextrins (CDs), there are two grades of Complexol i.e. Complexol B, and Complexol HP [4], these are molecular chelating agents belonging to a class of cyclic oligosaccharides which consist of (α-1,4)linked α-D-glucopyranose units. These compounds contain a lipophilic inner cavity and a hydrophilic outer surface. CDs have significant capacities to form inclusion complexes according to their core-shell structure. As a result of molecular complexation, these molecules are appropriate hosts to be used for drug-delivery, many industrial products, technologies and analytical methods. Natural CD and its synthetic derivatives can be employed to enhance certain physicochemical properties of the drug such as dissolution, solubility, stability or release rates. There are different derivatives of CDs, but β-CD is the most commonly used form, because it is easily produced and cheaper with respect to the others. Depending on the number of sugar units in cyclodextrins, the cavity size can be altered to accommodate different drugs. α, β, γ cyclodextrins refer to the sugar unit numbers of 6, 7 and 8, respectively. Apart from tailoring the cavity size, the solubility of cyclodextrins in aqueous medium can also be modified by hydroxypropyl, methyl or sulfa-butyl ether to derive the structure. Solubility and stability of various host agents of pharmaceutical agents, such as protein and peptide, steroids or low molecular weight agents, have been studied and improved by using natural or synthetic kinds of CD compounds. The inclusion complexation of this host-guest systems exhibits considerable intramolecular interactions, such as hydrogen bonding, hydrophobic attraction or electrostatic attraction [5][6].

Complexation Phenomenon: CDs are cyclic oligosaccharides of a glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to the lack of free rotation around the bonds connecting the glucopyranose units, the CDs are not perfectly cylindrical molecules but are toroidal or cone shaped. As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers by entrapping guest molecules in their internal cavity. No covalent bonds are formed or broken during drug CD complex formation, and in aqueous solution, the complexes readily dissociate and free drug molecules remain in equilibrium with the molecules bound within the CD cavity. [7]

ADVANTAGES OF COMPLEXOL:

1) Have high aqueous Solubility and Commensurately low viscosity.
2) Can reduce irritation on skin.
3) Odor and taste masking
4) Good solubilizing agent
5) Use as Complexing agent 6) Physio-chemically stable.
7) Chemically inert.
8) It is Free from Microbial contamination. [8][9]

DISADVANTAGES OF COMPLEXOL:

1) Nephrotoxicity
2) Diarrhea
3) Loss of appetite [10]

PHARMACEUTICAL APPROACHES OF COMPLEXOL:

1. Oral drug delivery
2. Nasal drug delivery
3. Rectal drug delivery
4. Topical application
5. Ocular delivery
6. Parenteral products [6] [10]

MATERIALS AND METHODS:

Drug (Telmisartan), Complexol B and Complexol HP Selectively taken from Gangwal chemicals Pvt Ltd, Tarapur, India., HCL, Methanol, Potassium dihydrogen phosphate, Disodium hydrogen phosphate.

For an investigation of physical and chemical properties of the drug substances alone Preformulation studies were done. Followed by Preparation of standard stock solution and calibration curve of Telmisartan (TLM). Series of dilution 2,4,6,8,10,12,14 ug/ml were prepared using phosphate buffer, pH 6.8 and 0.1 N HCl buffer (pH1.2). The absorbance at different concentration was taken at λ max 226 nm against blank. The standard calibration curve was obtained for data of concentration v/s absorbance. For the confirmation of API FTIR Spectroscopy, Differential scanning calorimetry study were done. After the conformation of Drug and Reagents Compatibility studies were taken place for that different concentration of drug and complexol for preparation of complexes by using inclusion complex technique.

The preparation of solid complexes of TLM and Complexol B / Complexol HP were performed by different techniques, which are described below. The different molar ratios (1:1,1:2, and 1:3) were kept to discuss solubility and which one forms a more stable complex.

Physical Mixture: Physical mixtures were prepared by homogeneous blending of previously sieved and weighed TLM and Complexol B / Complexol HP simply added in zip lock pouch and Shaked it.

Co-evaporation Method: TLM and Complexol B / Complexol HP was taken in different ratios (1:1,1:2,1:3) in 10 ml of 50% aqueous ethanol. The solution was stirred till clear solution was obtained and the resulting solution was evaporated under vacuum at a temperature of 45ºC. the solid residue was further dried completely at 45ºC for 48 hours. The dried complex was pulverized into a fine powder and sieved through sieve no.60. the resulting samples were stored in a desiccator until further use.

Kneading Method: Complexol B / Complexol HP was taken (in different ratios 1:1,1:2,1:3) in a mortar and 10 ml of 50% ethanol was added and triturate to get slurry. Then, slowly drug was incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25ºC for 24 hours. Pulverized and passed through sieve no.60. the resulting samples were stored in a desiccator until further use.

Prepared complexes were evaluated according to Micrometrics properties, solubility, Drug content, Differential Scanning Calorimetry (DSC) studies, Powder X-ray diffraction, FTIR Study, Scanning electron microscopy, *in-vitro* dissolution studies of TLM, inclusion complexes and marketed formulation were performed using USP dissolution apparatus type II (paddle type).

RESULT AND DISSCUSSION:

The Phase solubility diagram was obtained by measuring the molar concentration of the TLM in the presence of Complexol B and Complexol HP at various concentrations (0-10 mMol), as shown in fig.22. the solubility of TLM linearly increased as a function of Complexol concentration, as Complexol concentrations increased from 0-10 mMol/L which are plotted on table no.18. the enhancement in the solubility of TLM confirmed intermolecular interactions existed between the host and the guest. Furthermore, the profile of all diagrams could be classified as A_L type according to the method reported by Higuchi and Conners, indicating 1:1 molecular complex formation.

The apparent stability constant (K) of the host- guest complex could be an indication for probing the binding strength between the host and guest molecule. K values of Complexol: TLM complexes (1:1) were calculated from the linear plots of the phase solubility diagram and shown in table no.19.The inclusion stability rate constant (Kc) was calculated as 1.30 and 2.99 L/mMol for the complexation between TLM and Complexol B and Complexol HP resp.

From the data confirmed that a favourable interaction occurred between TLM and Complexol HP. It has been reported that solubility and oral bioavailability is improved when the Kc value is in between 200 and 5000 M^{-1}(Higuchi and Connors 1965). Hence, the stability rate constant of TLM and Complexol HP complexation verifies the most stable complex formation in an aqueous solution as it has higher value than Complexol B. Therefore, in light of the phase solubility data, Complexol HP was selected as the optimal Complexol to form the TLM inclusion complex formulation.

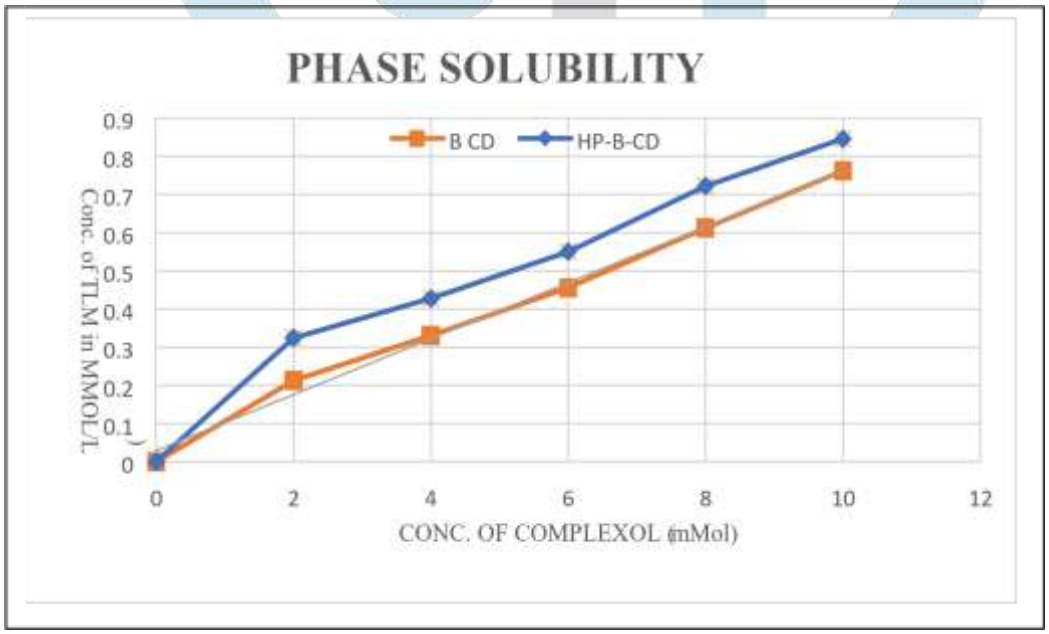


Fig.no.01. Phase solubility diagram of Complexol B and Complexol HP

TLM complexes are prepared by using co-evaporation method and kneading method in different molar ratios of Complexol B and HP given in table.

Table 1: Preparation of complex

SR. NO.	BATCH	WEIGHT RATIO	COMPLEXOL USED	METHOD OF PREPARATION OF COMPLEXES:
1	C_1	1:1	COMPLEXOLB	Co-evaporation method
2	C_2	1:2	COMPLEXOLB	
3	C_3	1:3	COMPLEXOLB	
4	C_4	1:1	COMPLEXOL HP	
5	C_5	1:2	COMPLEXOL HP	
6	C_6	1:3	COMPLEXOL HP	
7	C_7	1:1	COMPLEXOLB	Kneading method
8	C_8	1:2	COMPLEXOLB	
9	C_9	1:3	COMPLEXOLB	
10	C10	1:1	COMPLEXOL HP	
11	C11	1:2	COMPLEXOL HP	
12	C12	1:3	COMPLEXOL HP	

Complexes were prepared by using co-evaporation method and kneading method to check solubility enhancement studies. The enhancement in the solubility of complex is mainly attributed to the formation of stable inclusion complex of TLM with Complexol. complex of prepared batch C_{11} and C_{12} exhibits higher ratio, hence complexol HP may enhance more solubility as compared to Complexol B.

Table 2: solubility studies of Prepared complexes

SR.NO.	BATCH	Solubility (mg/ml)	Solubility Enhancement Ratio
1	C_1	0.324 ± 0.23	2
2	C_2	0.356 ± 0.2	3
3	C_3	0.415 ± 0.12	4
4	C_4	0.510 ± 0.45	5
5	C_5	0.703 ± 0.15	7
6	C_6	0.738 ± 0.14	7
7	C_7	0.808 ± 0.11	8
8	C_8	0.845 ± 0.47	8
9	C_9	0.857 ± 0.25	8
10	C10	0.721 ± 0.13	7
11	C11	0.815 ± 0.22	8
12	C12	0.921 ± 0.19	9

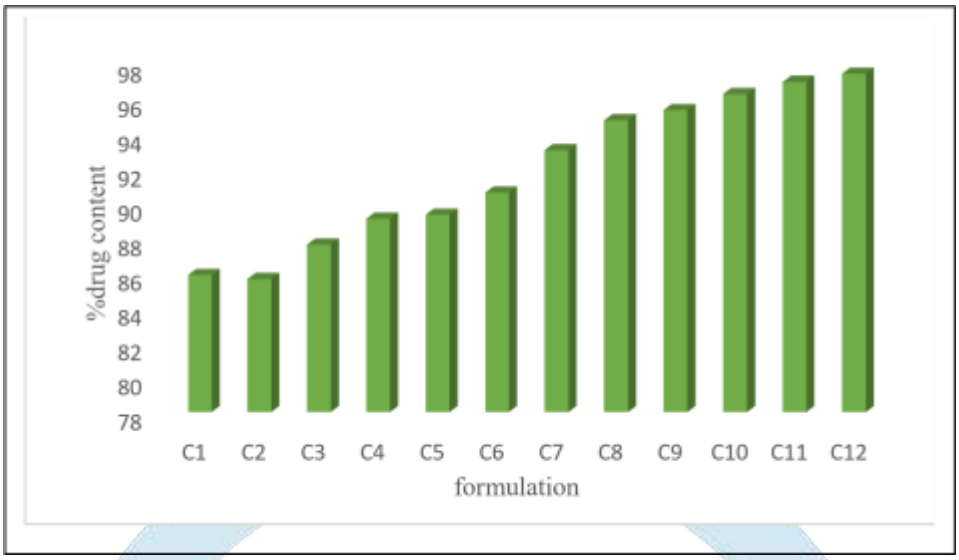


Fig. No. 2 Percent drug content

The percentage yield and percentage drug content of prepared batches were given in Fig no.2, batch C_{12} shows higher drug content and their practical yield also maximum than others. As C_{12} batch shows higher concentration of complexol HP it gives maximum results.

The percentage drug release vs time profiles for the systems under study in 0.1N HCl buffer (pH 1.2) and phosphate buffer (pH 6.8) shown in graph

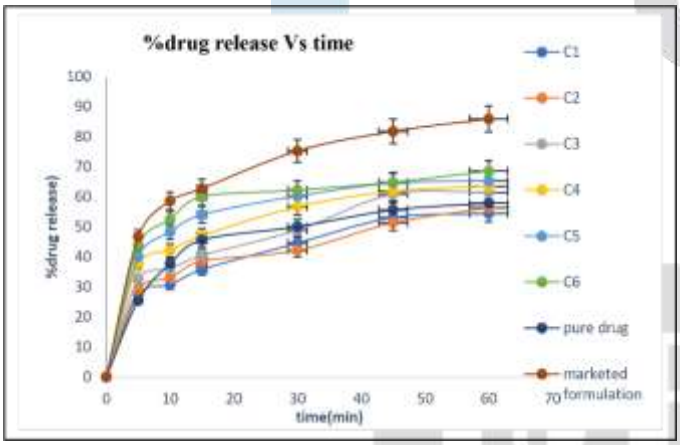


Fig. No.3.Cumulative % drug release of prepared complexes (C_1-C_6), pure drug and marketed formulation in phosphate buffer, pH 6.8

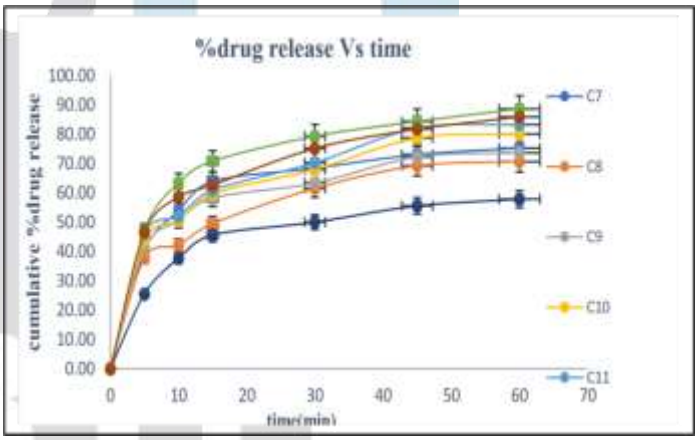


Fig. No.4. Cumulative % drug release of prepared complexes (C_7-C_{12}), pure drug and marketed formulation in phosphate buffer, pH 6.8.

Above Graph illustrate the percentage drug release vs time profiles for the systems under study in 0.1 N HCL buffer (pH 1.2) and phosphate buffer, pH6.8. In 0.1 N HCL, TLM is poorly soluble with 30 % of the drug dissolving in 60 min. complexes prepared by co evaporation method (C_1-C_6 batch), shows 68% of maximum drug release in 60 min (of C6 batch) and complexes prepared by kneading method (C_7-C_{12} batch), shows 91% of maximum drug release in 60 min (C12 batch). Increase in % drug release is due to increase in concentration of complexol, obviously due to drug – complexol HP/ complexol B inclusion complex formation. According to table no. 24 and 25, Complexol HP gives better results than complexol B.

TLM showed extremely poor dissolution in phosphate buffer, pH6.8 with 25% of drug dissolving in 60 min. all the kneaded and co evaporated systems showed significant improvement in dissolution as compared with TLM. complexes prepared by co evaporation method (C_1-C_6 batch), shows 75% of maximum drug release in 60 min (of C_6 batch) and complexes prepared by kneading method (C_7-C_{12} batch), shows 88 % of maximum drug release in 60 min (C_{12} batch). Batch C_{12} shows better results of inclusion complex formation of TLM with Complexol HP, as confirmed by FTIR, XRD, SEM and DSC.

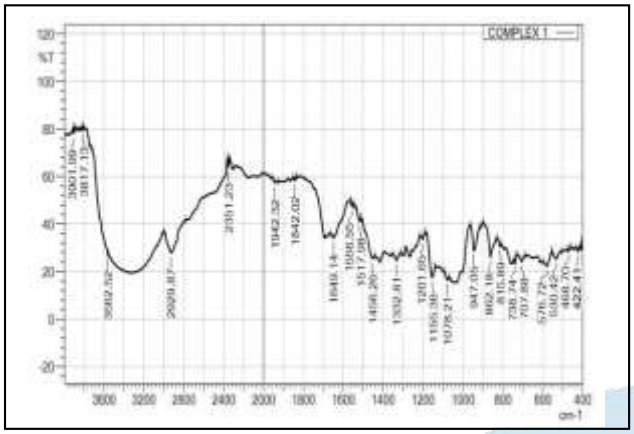


Fig.No.5 Telmisartan (inclusion complex ii)FTIR spectra of Complexol HP:

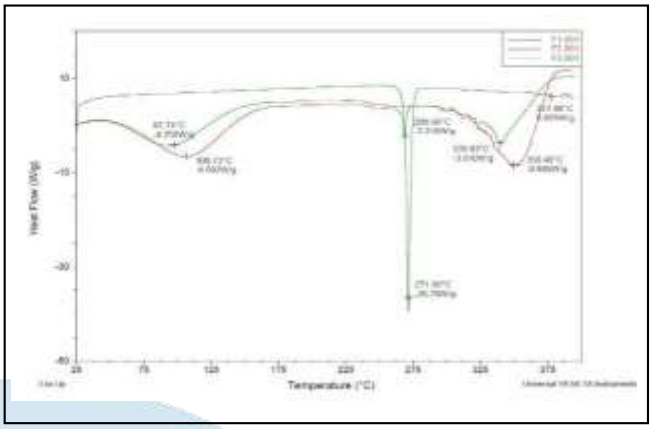


Fig. No. 6 DSC analysis of Telmisartan, complexol

HP and prepared complexes

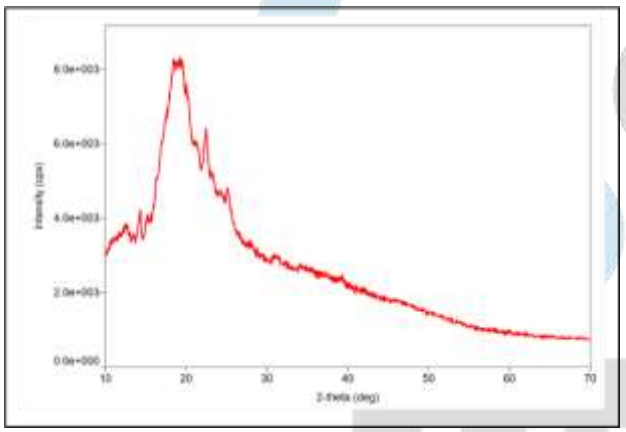
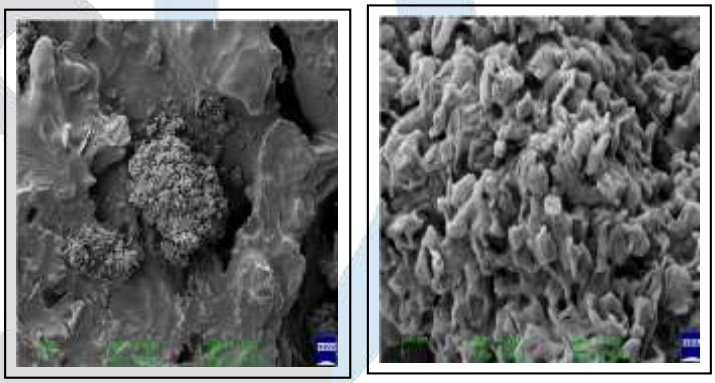


Fig No.7. XRD of TLM: Complexol HP complex (kneading method)



Figu No.8. scanning electron microscopy of prepared complex (C_{12} Batch)

STABILITY STUDIES:

The results of stability studies shown that there were no significant changes in the pH, drug content and in vitro dissolution study of complexes, after storing at a room temperature of 40ºC ±2ºC/75% ±5% relative humidity for One month. The best formulation (C_{12} batch) was subjected to short -term stability study by storing the formulations at 40ºC and 75% RH up to 6 weeks. After the time period, the prepared complexes were analysed for %drug content and *in vitro* dissolution study.

In this project work , inclusion complexes of Telmisartan with B-CD and HP-B-CD have been successfully prepared. The solubility of TLM in water was significantly increased in an average of 2 and 8 fold for B-CD and HP-B-CD ,resp. Results showed that the kneading method yielded higher degree of amorphous entities suggesting the formation of inclusion complexes between TLM and B-CD and HP-B-CD. Phase solubility studies indicated stable inclusion complexes and used to compare the solubilization effect of B-CD and HP-B-CD to Telmisartan. In medium like (0.1 N HCl Ph 1.2 and phosphate buffer pH 6.8) Dissolution profiles showed that all the complexes exhibit higher dissolution rate than those of the physical mixtures and TLM alone. The dissolution of TLM was substantially higher for B-CD and HP-B-CD inclusion complexes prepared by kneading method. Thus, the method of preparing complexes played a key role in enhancing the dissolution rate . Therefore, the kneaded system of TLM with HP-B-CD prepared at a molar ratio of 1:3 could be chosen as the best formulation of complexes for better solubilization capacity of HP-B-CD , compared to B-CD .

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