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ORAL DISINTEGRATING TABLETS OF CILOSTAZOL-HP-β-CD INCLUSION COMPLEX

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Keywords:

Cilostazol, hydroxypropyl-β-cyclodextrin, spray drying, orally disintegrating tablets, Pearlitol SD-200, Kollidon CL

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ABSTRACT: Low solubility and biovariability associated with cilostazol (CLZ) pose serious formulation problems despite several advancements in dosage form design. The present research work amalgamates two different solubility enhancement techniques, viz. spray drying and cyclodextrin inclusion complexation to produce amorphous composites of CLZ with increased solubility and dissolution characteristics. FTIR studies unveiled inclusion/ interaction of cyclohexane ring and tetrazole moiety of CLZ in the hydroxypropyl-beta-cyclodextrin (HP-β-CD) cavity. Thermal analysis by DSC showed a decrease in melting points of CLZ and HP-β-CD, indicating favorable complex formation. P-XRD studies revealed reduction in crystallinity and amorphization of CLZ in the complex. SEM indicated a drastic change in surface morphology compared to pure CLZ. These complexes were compressed into oral disintegrating tablets (ODTs) using direct compression technique. The ODTs were characterized for disintegration time, wetting time and *in vitro* dissolution. Remarkable improvement in solubility and *in vitro* dissolution characteristics was observed for ODTs in water and compendial dissolution media. Inclusion complexation with HP-β-CD, amorphous composites produced by spray drying technique and the use of multi-functional co-processed excipients like Pearlitol SD-200, Kollidon CL and MCC-200 are responsible for increased solubility and dissolution of CLZ

INTRODUCTION: Cilostazol is a phosphodiesterase III inhibitor with therapeutic focus on cAMP. It exerts its vasodilatory action by inhibiting platelet aggregation induced by collagen, 5'-adenosine diphosphate (ADP), epinephrine, and arachidonic acid [1, 2]. CLZ is primarily used in the treatment of intermittent claudication (IC) which is the primary symptom of peripheral arterial disease (PAD). Around 12 million people in USA alone have PAD, and as the world population is aging, the incidence is expected to rise [3]. The best medical therapy for IC has only four drugs on its panel, amongst which CLZ has been approved by the US FDA [4, 5].

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CLZ is a typical BCS class II molecule and thereby inherits poor solubility, wettability, dissolution characteristics and variable pharmacokinetic parameters which limit its clinical efficacy. Like most other lipophilic drugs, co-administration of high fat meal has shown significant increase in the rate and extent of CLZ absorption [6, 7]. Its absorption in the GIT is slow, variable, and incomplete. The absolute bioavailability of CLZ is not known and relative bioavailability is unpredictable [8].

The marketed formulations of CLZ mostly include conventional immediate release tablets. Elderly people find it inconvenient to ingest these dosage forms owing to a drop down of the function of feeding/ swallowing with age. In addition, dysphagia is observed as an after effect in some patients with cerebral infarction. This leads to patient non-compliance and prolongs the duration of treatment. Formulating an orally disintegrating tablet (ODT) of CLZ can solve both the above

issues. ODTs disperse or dissolve in the saliva and can be swallowed without water, thus providing patient compliance to the elderly [9]. Moreover, ODTs have the potential to increase the bioavailability of poorly soluble drugs which exhibit dissolution rate limited absorption [10].

Conventional techniques like solid dispersion, inclusion complexation, co-solvency, hydrotropy, etc. have been reported to enhance the solubility of poorly soluble drugs, but only to a limited extent and have meager effect on pharmacokinetic variability [11]. Recent advancements in dosage form design focus on particle engineering and the use of multifunctional excipients to manipulate the poor solubility/ hydrophobicity associated with these molecules. Applications of combinatorial techniques, viz. size reduction-spray drying, solid dispersions-spray drying, lipid based excipients-freeze drying, each of which has its own mechanism of solubility enhancement act in synergism to overcome or nullify the solubility and biovariability issues.

One such technique, amorphous composites has been used here to increase the solubility and characterisitcs of CLZ. Cyclodextrins (CDs) and its derivatives are termed as molecular-containers that host molecules of different polarities and molecular weights within their cavity [12, 13]. HP-β-CD, a modified analog of β-CD with 2-hydroxypropyl unit, has been used in this study. It is widely studied in the field of pharmaceuticals owing to its ability to enhance solubility by producing wettable amorphous compounds with increased complexing power and minimal toxicity [14-16]. Lack of in-depth data about the CLZ-HP-β-CD systems and unavailability of dosage forms in the market using this technique, prompted us to adopt this technique for developing ODTs.

Therefore, we explore the combinatorial spray drying-inclusion complexation technique for complex formation in contrast to the conventional methods reported in the earlier paper [17]. A detailed characterization of these complexes has been carried out to understand the mode of interaction of CLZ with HP-β-CD and crystallinity of the complex. FTIR and DSC have been used to confirm complex formation. P-XRD and SEM studies have been utilized to understand the crystallinity of the formed complex. Subsequently, these complexes were formulated as ODTs by direct compression technique. The tablets were evaluated for drug content, hardness, friability, porosity, disintegration time, wetting time, etc.

MATERIALS AND METHODS:

Materials:

CLZ was obtained from Ipca laboratories, Mumbai. HP-β-CD and Sodium starch glycolate (Glycolys) were received as gift samples from Roquette chemicals, Mumbai. Crospovidone, Ludipress and Ludiflash were gifted by BASF, Mumbai. Other excipients used were Kiccolate ND-200 (Asahi Kasei chemicals), Granulac 200, Flowlac 100 (Meggle Pharma), MCC 200, Mannitol (FMC Biopolymer), Croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer) and magnesium stearate. All other reagents used were of analytical grade.

Analytical method:

A validated stability indicating assay method was used for determination of CLZ [18]. The HPLC apparatus (Perkin Elmer, Series 200 EP) was equipped with binary pump, an autosampler and photodiode array (PDA) detector. A C-18 Inertsil column (4.6 * 250 mm, 5 µ) was used. The mobile phase comprising of water: acetonitrile (ACN) (50:50 v/v) was run at 1 ml/min with an injection volume of 20 µl at detection wavelength of 257 nm.

The retention time of CLZ was 7.88 ± 0.05 minutes. The mean regression equation for CLZ was y = 37013x (r = 0.9996, n=6) in the concentration range of 1-160 µg/ ml, wherein y is the peak area and x is the concentration of CLZ.

Preparation and evaluation of solid binary systems:

Preparation of physical mixtures of CLZ and HP-β-CD:

Physical mixtures (PMs) of CLZ and HP-β-CD were prepared in 1:2 molar ratios. Both the ingredients were weighed separately, passed through 100 mesh sieve and mixed manually.

Preparation of inclusion complex (IC) of CLZ and HP-β-CD by spray drying technique:

CLZ and HP-β-CD were weighed in terms of their molar ratios (1:2) obtained from phase solubility studies and Job's plot. Hydro-alcoholic solution containing ethanol and water in 75:25 ratio was used as solvent for spray drying. 75 ml ethanolic solution of CLZ was added to 25 ml aqueous solution of HP-β-CD under continuous stirring to obtain a clear solution. The resulting solution was sonicated for 10 minutes and then stirred for 3-4 hours using magnetic stirrer at 30 ºC. The feed was sprayed in the spray dryer (LabUltima-222) under continuous stirring.

The process parameters were so adjusted that maximum product concentrate was obtained in cyclone II of the spray dryer resulting in production of nanoamorphous composites with uniform size distribution. The yield of the spray-drying process was measured as the weight percentage of the powder obtained in the final operation compared with the amounts of solids (CLZ + HP-β-CD) present in the sprayed solution. The product thus obtained was collected, packed in aluminum foil and stored under dessicator until further use.

The optimized conditions for spray drying were as follows:

Inlet temperature: 75 ºC

Outlet temperature: 50 ºC

Cool temperature: 45 ºC

Inlet high temperature: 80 ºC

Outlet high temperature: 55 ºC

Spray rate: 1.5 ml/min

Atomization air pressure: 1.5 kg/cm^2

Aspirator flow rate: 50 Nm^3/hr

Batch size: 10% w/v

Characterization of inclusion complex:

Phase solubility studies and complexation efficiency:

Phase solubility studies of CLZ with HP-β-CD were performed in water according to the method reported by Higuchi and Connors [19, 20]. Excess amount of CLZ was added to the volumetric flask containing solutions of increasing concentrations of HP-β-CD (2mM to 16 mM). Each flask was capped and shaken on a rotary shaker for 24 hours at 30 ± 0.5 ºC to attain equilibrium, following which 5 ml aliquots of supernatant were withdrawn and filtered through 0.45µ whatman filter paper 1 ml aliquot of this filtrate was appropriately diluted with water and analyzed at 257 nm using a UV spectrophotometer. Phase solubility diagram was plotted with HP-β-CD concentration on X axis and CLZ concentration on Y axis. The stability constant (Ks) was calculated using the following formula,

$$K_s = \text{Slope} / S_0 (1-\text{slope}) \qquad \text{Eq. (1)}$$

where S_0 is the maximum solubility of drug in the absence of HP-β-CD

Complexation efficiency (CE) is defined as the solubilizing efficiency of CDs for guest molecule (in this case HP-β-CD and CLZ respectively). Based on the results of the phase solubility studies, CE of HP-β-CD for CLZ was determined using the following formula,

$$CE = [CLZ/HP\text{-}\beta\text{-}CD] / [HP\text{-}\beta\text{-}CD] = \text{Slope} / (1-\text{Slope}) \qquad \text{Eq.(2)}$$

where, [CLZ] and [HP-β-CD] are molar fractions of CLZ and HP-β-CD.

Continuous variation method (Job's plot):

Stoichiometry of the complex was determined by continuous variation (Job's) method [21]. Equimolar (0.05 mM) solutions of CLZ and HP-β-CD were prepared in methanol and water respectively. Varying quantities (ml) of CLZ and HP-β-CD solutions were mixed (1:9, 2:8, 3:7, ….., 9:1) keeping the final total volume to 10 ml. The samples were analyzed at 257 nm using UV spectrophotometer (Perkin Elmer Lambda 25). The difference in absorbance of CLZ in presence, and absence of HP-β-CD was plotted against R.

$$R = [CLZ]/ \{[CLZ] + [HP\text{-}\beta\text{-}CD]\} \qquad \text{Eq. (3)}$$

where, R = ratio of mole fractions of CLZ and HP-β-CD, where [CLZ] = Mole fraction of CLZ and [HP-β-CD] = Mole fraction of HP-β-CD.

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR is a very useful tool to prove the existence of both guest and host molecules in their complexes. FTIR spectra of CLZ, HP-β-CD, PM and IC were recorded in the range of 400-4000 cm^{-1} using

Perkin Elmer R*I spectrophotometer by KBr disc method.

Differential Scanning Calorimetry (DSC):
Thermal analysis of CLZ and its complexes was performed to confirm the polymorphic state of CLZ and to identify interactions between CLZ and HP-β-CD respectively. DSC thermograms of CLZ, HP-β-CD, PM and IC were recorded using ZYDIS calorimeter. About 1-3 mg of samples were sealed in flat bottomed aluminum cubicles and heated at a scan rate of 10 ºC/min from 30-300 ºC.

Powder X-ray diffractometry (P-XRD):
X-ray diffractograms of CLZ, HP-β-CD, PM and IC were recorded on a Philips Analytical X'pert Pro MPD with copper as anode using a voltage of 40 kV and a current of 35 mA. The diffractograms were recorded in 2θ angle range between 5 and 50º at a scanning rate of 1º/ min.

Scanning Electron Microscopy (SEM):
The scanning electron micrographs of CLZ, HP-β-CD, PM and IC were recorded using EvoLS10, Zeiss scanning electron microscope.

Formulation of ODTs:
Tablets containing 50 mg of CLZ or its equivalent amount of IC and suitable excipients were prepared by direct compression technique. The preliminary compositions of tablet formulations are shown in **Table 1**. All the excipients except magnesium stearate were previously sieved through 80 mesh screen and blended for 15 minutes. Magnesium stearate was passed through 40 mesh and added to the above blend. The final blend was lubricated for 5 minutes. The resulting mixture was directly compressed into tablets using a Rimek, 'B' tooling rotary tablet press equipped with flat faced 9 mm punches.

TABLE 1: ODT FORMULATIONS

	F1	F2	F3	F4	F5	F6	F7
CLZ-HP-β-CD (equivalent to 50 mg CLZ)	421.62	421.62	421.62	421.62	421.62	421.62	421.62
MCC 200	--	--	24.75	24.75	33.13	32.86	33.13
Granulac 200	93.73	--	--	--			--
Pearlitol SD 200	--	--	--	--	52.0	59.27	52.0
Ludipress	--	93.73	68.98	68.98	--	--	--
Ac-Di-Sol	--	--	--	--	--	--	--
Sodium starch glycolate	26.4	26.4	--	--	--	--	--
Ludiflash	--	--	26.4	--	35.0	--	--
Kiccolate ND-200	--	--	--	26.4	--	--	--
Kollidon CL	--	--	--	--	--	28.0	35.0
Magnesium stearate	8.25	8.25	8.25	8.25	8.25	8.25	8.25
Total weight (mg)	550.0	550.0	550.0	550.0	550.0	550.0	550.0

Evaluation of ODTs:
The prepared tablets were evaluated for drug content, hardness, friability, tablet porosity, disintegration time, wetting time, and dissolution profile.

Drug content:
Five tablets were accurately weighed and crushed using a mortar and pestle. Powder equivalent to 50 mg of CLZ was transferred to a 50 ml volumetric

flask and volume was made up with methanol. The sample was sonicated for 15 minutes, then filtered through 0.2µ filter and injected into HPLC system. The experiment was performed in triplicates. Drug content was expressed as % of the theoretical amount of CLZ, i.e. 50 mg.

Hardness:
Tablet hardness was evaluated by measuring the hardness of 10 tablets using Dr. Schleunizer 8M hardness tester.

Friability:
Tablet friability was evaluated using an Electrolab USP friabilator. Accurately weighed 10 tablets were tumbled at 25 rpm for 4 minutes. The tablets were then de-dusted, weighed, and the percent weight loss was calculated.

Tablet porosity:
Tablet porosities were determined according to the method reported by Latinen [22]. The tablet geometry was determined using a micrometer. The true densities of tablet components were determined with true density analyzer using helium as the measuring gas.

Wetting time:
Ten milliliters of water soluble dye eosin solution was added to petri dish containing five circular filter papers of 10 cm diameter. Tablets were carefully placed on the surface of the filter paper and the time required for water to reach upper surface of the tablet was noted as the wetting time [23].

Disintegration time:
This test was carried out in water as test solution using an electrolab disintegration apparatus. Six tablets were placed in the apparatus without a disk and the time required for complete disintegration of tablet was recorded.

***In vitro* dissolution studies of ODTs:**
In vitro dissolution profiles of ODTs was determined in 900 ml of 0.3% SLS in water as dissolution medium at 37 ± 0.5 °C using USP paddle apparatus (Electrolab) at 75 rpm. Five milliliters of samples were withdrawn at 5, 10, 15, 30, 45, 60 and 120 minutes and replaced with the same amount of fresh dissolution medium to maintain sink conditions. The solutions were immediately filtered through 0.2µ filter and analyzed using validated HPLC method.

RESULTS AND DISCUSSION:

Preparation and evaluation of spray dried complexes:

Optimization of spray drying process:
Spray drying produces smooth spherical particles with high specific surface area and low particle size. It is one of the most commonly used techniques for preparation of nano-amorphous solids from solutions [24-26]. Different organic solvents like DMSO, DMF and methanol were studied as solvent systems for spray drying. But, taking into consideration the solubility of individual components, yield of the product and environmental concerns associated with the use of organic solvent, the choice was zeroed down to hydroalcoholic solution containing ethanol and water. Ethanol:water (80:20) gave a clear solution containing CLZ and HP-β-CD in 1:2 molar ratio. Various process parameters like inlet air temperature, outlet air temperature, feed rate, atomization air pressure and aspirator speed were varied to understand the influence of each parameter on the maximum yield.

The inlet and outlet air temperatures were optimized at 75 and 50 °C, respectively, based on boiling points of the solvents used and stability of the drug to get dry and stable product. Effect of feed rate on the yield of the product was studied by increasing the feed rate from 1 ml/ minute up to 4 ml/ minute. There was marked decrease in the yield of the product with increase in feed rate. Maximum yield (71%) was obtained at feed rate of 1.5 ml/ minute. Atomization air pressure and aspirator flow rate were optimized at 1.5 kg/cm^2 and 50 Nm^3/hr respectively to achieve maximum yield and decrease the processing time.

All the above parameters were so adjusted that maximum product concentrate could be obtained in cyclone II of the spray dryer. Spray drying produced free flowing complexes with significantly less moisture content (2-4% as determined by Karl-Fischer technique) compared to pure HP-β-CD (10% w/w). The spray dried complexes so obtained

in cyclone II were in nanosized range with narrow size distribution.

Characterization of inclusion complex:

Phase solubility studies:

Phase-solubility diagrams are generally used to calculate stoichiometry of drug/cyclodextrin complexes. Phase solubility studies exhibited an A_L type curve indicating formation of soluble complexes of first order with respect to HP-β-CD and first or higher order with respect to CLZ. There was a linear increase in solubility of CLZ with an increase in HP-β-CD concentration as seen in **(Figure 1)**. Binding strength of the complex was determined using stability constant values and the apparent 1:1 stability constant, K_s was found to be 892.13 M^{-1} (usual range 100-20000 M^{-1}). Higher value of K_s indicates good complexation of CLZ with HP-β-CD.

Generally, it is observed that poorly soluble drugs show non-linear trend in the phase solubility diagram. Complexation efficiency is regarded as a more accurate method for determination of the solubilizing efficiency of CDs because it is independent of both the intrinsic solubility of the drug and the intercept of phase solubility diagram [27]. The complexation efficiency of CLZ-HP-β-CD complex was found to be 3.61 x 10^{-3}.

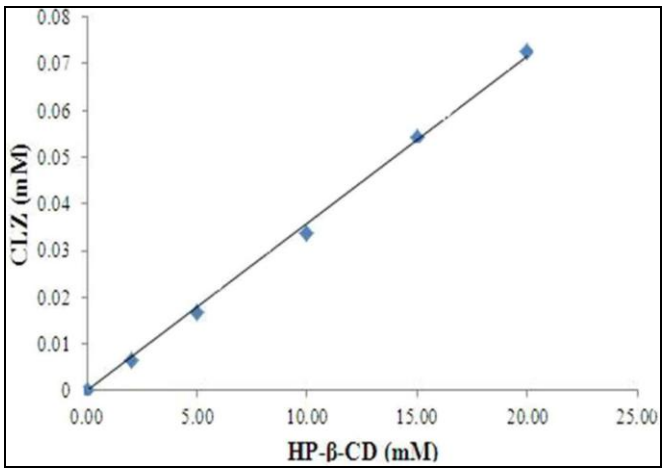

FIGURE 1: PHASE SOLUBILITY DIAGRAM OF CLZ-HP-β-CD SYSTEM IN WATER.

Continuous variation method (Job's plot):

Stoichiometry of drug/cyclodextrin complexes cannot be derived from simple phase-solubility studies, especially for poorly soluble drugs. Therefore, Job's plot is preferred over phase solubility studies for determining stoichiometry of drug:cyclodextrin complexes [28]. According to the continuous variation Job's method, change in absorbance is directly related to the concentration of complex, and can be measured for a set of samples with continuously varying the molar fraction of the components. The maximum concentration of the complex will be present in the sample where the molar ratio R corresponds to the complexation stoichiometry. The maximum absorbance of CLZ-HP-β-CD was observed for R = 0.7 (**Figure 2)**, which indicates 1:2 stoichiometry.

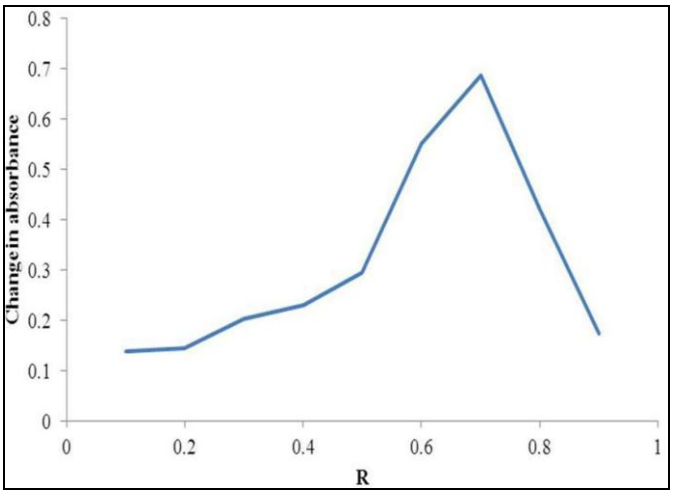

FIGURE 2: JOB'S PLOT DETERMINING STOICHIOMETRY OF CLZ-HP-β-CD INCLUSION COMPLEX.

FTIR spectroscopy:

FTIR spectrum of CLZ was characterized by aromatic C=O stretching of the amide band at 1668 cm^{-1}, tetrazole moiety at 1504 cm^{-1}, N=N stretching of the tetrazole moiety at 1295 cm^{-1}, aromatic ether at 1196 cm^{-1}, NH stretching of the quinolinone moiety from 3330-3060 cm^{-1} and NH bending of the quinolinone moiety from 1570-1515 cm^{-1}. FTIR spectrum of HP-β-CD showed broad absorption bands at 3383 cm^{-1} (symmetric and anti-symmetric O-H stretching), 2929 cm^{-1} (CH_2 aliphatic stretch), 1155 cm^{-1} (C-H stretching) and 1034 cm^{-1} (C-O-C bending vibrations) [29,30].

The spectrum for PM of CLZ–HP-β-CD was superimposable to those of the pure compounds with attenuation of the CLZ peaks as shown in (**Figure 3)**. The shifts in the IR bands of CLZ and HP-β-CD in the CLZ-HP-β-CD IC are shown in **Table 2**. The insertion of cyclohexane ring of CLZ into the electron rich cavity of HP-β-CD increases

the density of electron cloud, resulting in high frequency shifts. On the other hand, decrease in the frequency between IC and its constituent molecules may be due to the formation of hydrogen bonds and presence of van der Waals forces between CLZ and HP-β-CD. Thus, FTIR spectra prove the formation of CLZ–HP-β-CD IC.

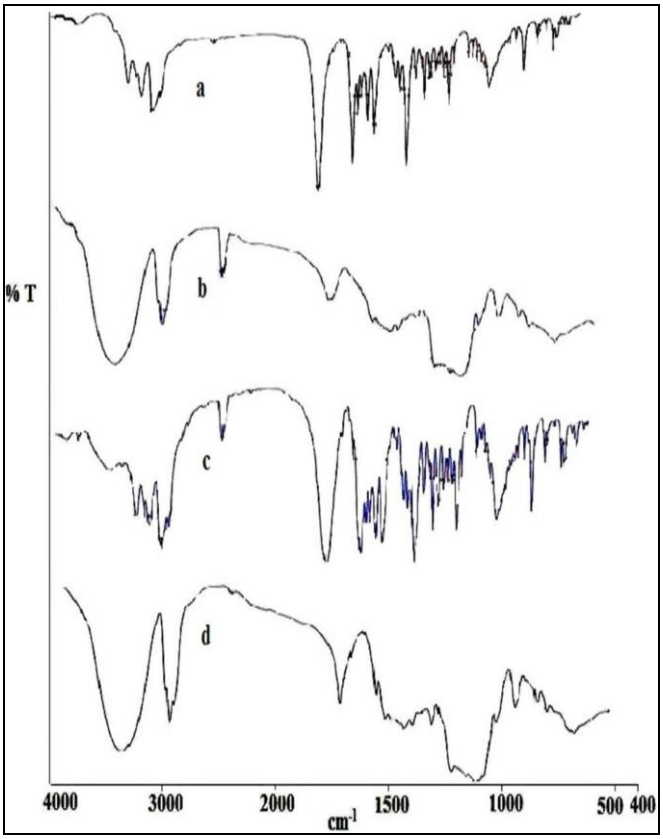

FIGURE 3: FTIR SPECTRA OF A) CLZ, B) HP-β-CD, C) CLZ-HP-β-CD PM AND D) CLZ-HP-β-CD INCLUSION COMPLEX.

TABLE 2: SHIFTS IN IR FREQUENCIES OF CLZ AND HP-β-CD IN COMPLEX.

Group assignment	Wave number (cm^{-1})		Δ (cm^{-1})
	CLZ	CLZ in complex	
C=O (Amide)	1668.11	1668.43	-0.32
Tetrazole	1505.35	1504.51	+0.84
N=N	1295.62	1295.43	+0.19
Ar-O-C	1196.86	1196.45	+0.41
Group assignment	**Wave number (cm^{-1})**		**Δ (cm^{-1})**
	HP-β-CD	**HP-β-CD in complex**	
-OH stretching	3383.28	3374.19	+9.09
-CH stretching	2929.80	2931.85	-2.05
C-H stretching	1155.12	1155.45	-0.33
C-O stretching	1083.09	1080.09	+3.00
C-O-C bending	1032.16	1037.75	-5.59

Differential Scanning Calorimetry studies:

DSC thermograms of CLZ, HP-β-CD, PM and IC are shown in **(FIGURE 4)**. The CLZ thermogram showed a sharp endothermic peak at 159-162 ºC corresponding to its melting point. DSC thermogram of HP-β-CD showed a broad endotherm in the range of 65-125 ºC, which can be attributed to desolvation of water molecules present in the HP-β-CD cavity [31]. Thermal curves of PMs of CLZ with HP-β-CD showed endothermic peak of CLZ with lower area, lower H_{fus} and a shift in the endothermic peak to a slightly lower temperature. In PM there is almost 50% reduction in the height of CLZ peak indicating slight interaction. The endothermic peak of CLZ disappeared in the inclusion complex, indicating strong interactions of CLZ and HP-β-CD. This could be attributed to the formation of an amorphous solid, encapsulation of CLZ inside the HP-β-CD cavity, or both [32].

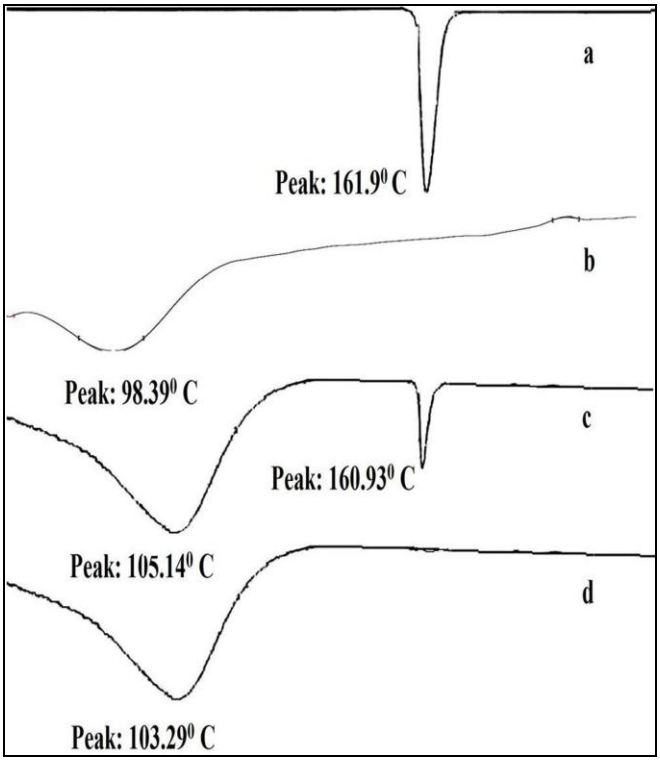

FIGURE 4: DSC THERMOGRAPHS OF A) CLZ, B) HP-β-CD, C) CLZ-HP-β-CD PM AND D) CLZ-HP-β-CD INCLUSION COMPLEX.

Powder X-Ray Diffractometry:

The change in crystallinity of CLZ on complexation with HP-β-CD was studied using P-XRD. The P-XRD diffractograms of CLZ, HP-β-CD, PMs and ICs are shown in **(Figure 5)**. The

crystalline nature of CLZ was evident from the presence of intense peaks in the diffractogram at 12.67º, 12.98º, 15.35º, 15.76º, 17.98º, 18.71º, 19.59º, 22.19º and 22.58º. The P-XRD pattern of HP-β-CD presents only an amorphous halo due to its non- crystalline nature [33]. The diffractogram of PM exhibits most of the principle peaks of CLZ along with the amorphous halo of HP-β-CD, indicating slight or no interaction between the pure components.

In contrast to these observations, IC showed a spectrum similar to that of amorphous HP-β-CD and the disappearance of characteristic crystalline peaks of CLZ. The diffraction pattern of the peaks of IC was more diffused as compared to pure components. The decrease in intensity and FWHM values for IC's compared to plain CLZ indicate the transformation of CLZ from crystalline to amorphous state in the complex [34].

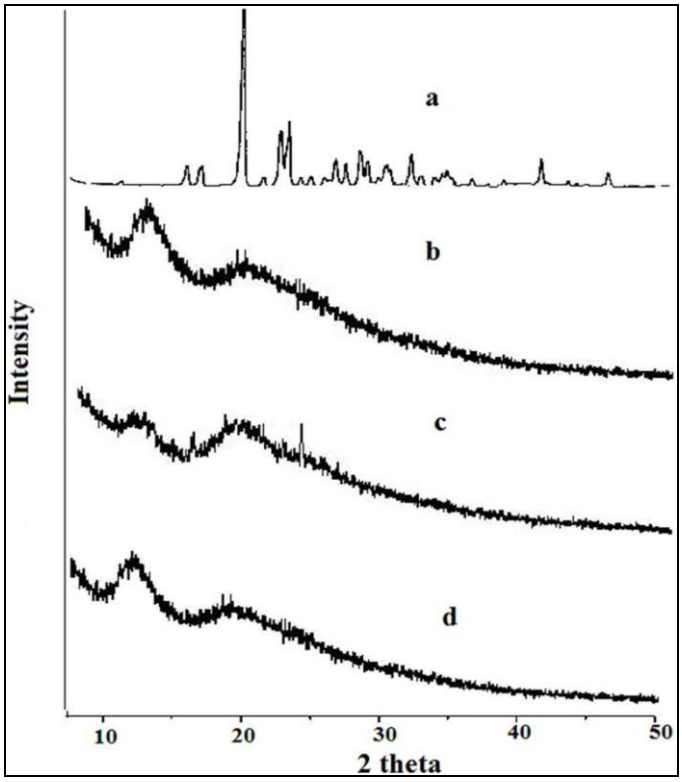

FIGURE 5: P-XRD SPECTRA OF A) CLZ, B) HP-β-CD, C) CLZ-HP-β-CD PM AND D) CLZ-HP-β-CD INCLUSION COMPLEX.

Scanning Electron Microscopy:

SEM gives an indication of the crystalline nature of drug in the complex [35]. Scanning electron micrographs of CLZ, HP-β-CD, PM and IC are shown in **(Figure 6)**. CLZ appeared as prismatic crystals while HP-β-CD showed the characteristic amorphous spherical shape. SEM image of PM exhibited the characteristic CLZ crystals, mixed with HP-β-CD particles or adhered to their surface, thus confirming the presence of crystalline drug. In IC, the original morphology of both individual components disappeared and thus it was not possible to distinguish the presence of either CLZ or HP-β-CD.

There was a drastic change in the surface morphology of IC indicating formation of a new solid phase, which results from the complexation between CLZ and HP-β-CD.

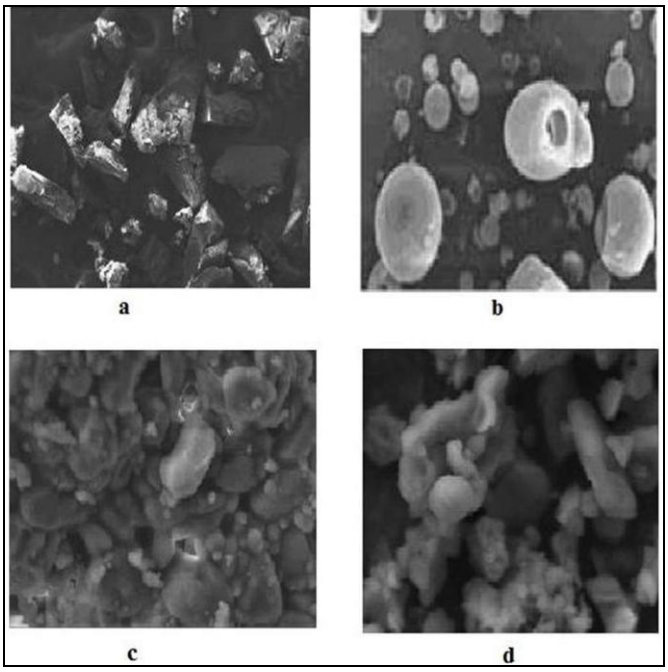

FIGURE 6: SEM IMAGES OF A) CLZ, B) HP-β-CD, C) CLZ-HP-β-CD PM, D) CLZ-HP-β-CD INCLUSION COMPLEX.

Formulation of ODTs:

Trials were conducted with different disintegrants viz. sodium starch glycolate, ludiflash, kiccolate ND-200 and kollidon CL. Granulac 200, pearlitol SD 200 and ludipress were used as diluents for the above trials.

DT and WT are important criterion for selecting an optimal formulation for ODTs. It reflects water uptake of the dosage form and is closely related to the hydrophilicity of excipients and the inner structure of the tablets. Sodium starch glycolate and cros-carmellose sodium both exhibit their disintegrant mechanism via swelling [36]. They lack a

highly porous structure and hence do not swell readily. Moreover, they form a viscous gel around the core, when in contact with water [37].

This retards complete disintegration and thereby rapid dissolution of CLZ. Similarly, ludiflash, a lactose based excipient also forms gel in contact with water. Therefore, it is recommended to use ludiflash with small amounts of kollidon CL to impart disintegrant properties [38]. According to the formulations F7 containing 9% w/w of kollidon CL had the least DT. The porous particle morphology of kollidon CL resulted in rapid uptake of water into tablet core by capillary mechanism, yielding rapid volume expansion and hydrostatic pressures that finally result in rapid disintegration [39-41].

Pearlitol SD 200 utilized in the formulation is a directly compressible grade of mannitol. Granulac 200 is another grade of lactose with good compactibility. It was observed that formulations containing granulac showed higher DT and WT compared to those containing pearlitol. At the initial stage of dissolution, CLZ dissolved from formulation containing granulac was slower than formulation containing pearlitol. This effect could be explained by the surface free energy and compressibility characteristic of both the ingredients. Lactose and mannitol have low and high surface free energy respectively [42].

Further, lactose contains more hydroxyl group (6) compared to mannitol (6). These factors contributed to stronger cohesion force between particles of lactose than mannitol, which contributed to lengthening of DT in granulac based formulation. Higher compression force required to attain appropriate hardness in granulac based formulation resulted in lower tablet porosity, thereby prolonging the process of water penetration, resulting in increased values of DT and WT [43].

Pearlitol SD 200 has good flowability and provides a refreshing or cooling sensation due to negative heating. One of the most desirable properties of Pearlitol SD 200 is that it dissolves rapidly without increase in viscosity, thus accelerating the process of disintegration [44]. MCC 200 has excellent compactibility, thus maximizing the pore structure of tablet matrix. It also provides good flowability and can promote disintegration of the tablets [45].

Trial F7 containing pearlitol SD 200 (9.45%), MCC 200 (6.02%), kollidon CL (6.36%) and magnesium stearate (1.50%) gave the least DT (23 secs.), WT (20 secs.) and 90% dissolution in 15 minutes. A comparative dissolution profile and evaluation parameters are presented in **Table 3** and **(Figure 7)**.

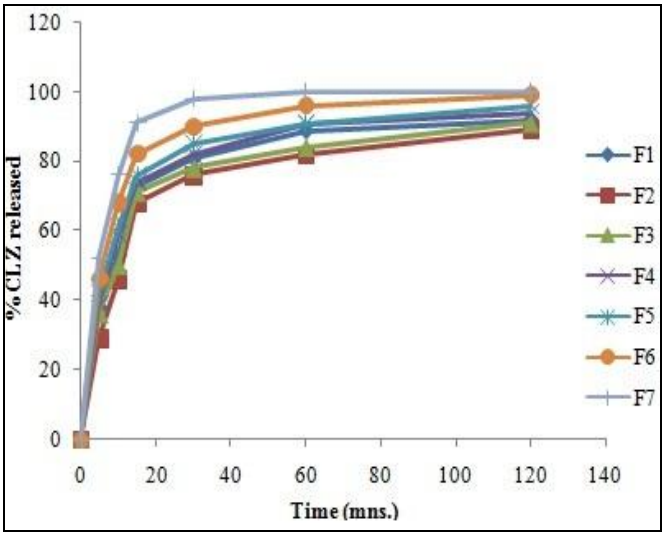

FIGURE 7: DISSOLUTION PROFILES OF DIFFERENT BATCHES OF ODTs.

TABLE 3: EVALUATION OF ODTs.

	F1	F2	F3	F4	F5	F6	F7
Thickness (mm)	4-4.2	4-4.2	4-4.2	4-4.2	4-4.2	4-4.2	4-4.2
Hardness (N)	40.2±1.1	41±1.4	40.8±0.5	41.2±0.9	40.4±0.8	41.1±0.7	41.2±1.3
Friability (%)	0.58±0.08	0.61±0.05	0.52±0.06	0.58±0.04	0.62±0.04	0.54±0.04	0.52±0.06
DT (s)	38.1 ± 1.8	45.1±1.2	41.3 ± 1.1	39.6± 1.6	35.2±1.8	26.3±1.8	23.1±1.8
WT (s)	38.9 ± 1.2	44.8±1.3	39.9 ± 1.7	38.2 ± 1.2	34.1±1.4	25.1±0.9	20.2±1.4
Compression force (kN)	7.0	7.2	7.0	6.9	6.7	6.7	6.5
Tablet porosity (%)	19.98±1.1	16.1±1.6	18.6±1.2	19.8±1.4	21.1±1.3	21.9±1.1	23.5±1.2
Assay (%)	99.1±1.1	98.7±0.9	100.8±0.7	99.8±1.2	99.2±1.3	101.1±0.8	99.8±1.6
Dissolution ($T_{15\ mins.}$)	73.1 ± 1.1	67.9 ± 1.4	71.1±1.8	73.9±1.6	76.2±1.5	81.3±1.9	90.7±1.5

CONCLUSION: The unique concept of synergistically combining two different solubility enhancement strategies, viz. spray drying and cyclodextrin inclusion complexation brought about a significant increase in the solubility and dissolution profile of CLZ. Robust analytical techniques such as FTIR, DSC, P-XRD and SEM confirmed formation of cyclodextrin included amorphous composites of CLZ. The use of co-processed excipients like PearlitolD-200, MCC-200 and Kollidon CL increased the porosity and resulted in rapid disintegration of the ODTs.

Therefore a combination of mechanism like inclusion complexation, amorphization of CLZ in the complex and use of multi-functional excipients resulted in enhancement of solubility and dissolution characteristics of CLZ. Thus, the use of nano-amorphous composites of CLZ proves to be a potential dosage form design for oral drug delivery of CLZ by providing patient compliance, especially to geriatrics.

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