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Research Article

Preparation and *In-Vitro* Characterization of Crystallo-Co-Agglomerates of Cilnidipine

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ABSTRACT
The present invention was aimed to develop pharmaceutically equivalent, stable, cost effective and quality improved formulation of cilnidipine with enhanced dissolution rate and micromeritic properties by preparation of agglomerates using a novel crystallo-co-agglomeration technique using water and DCM as bad and good solvent respectively. The influence of various polymers and different experimental conditions on formation of crystallo-co-agglomertaes(CCA) was evaluated. To optimized the agglomerates of desired characteristics 3^2 factorial design was implemented. The crystallo-co-agglomerates obtained having improved dissolution rate and micromeritic properties than pure drug. The optimized batch of CCA containing cilnidipine was characterized by FTIR, DSC, SEM, XRD and GC-HS which illustrated that there is no interaction between drug and excipients and negligible amount of residual solvent. Hence at last we conclude that this technique may be applicable for producing solid oral dosage form of cilnidipine with improved dissolution rate and oral bioavailability. However in-vivo studies are required to confirm these results.
Keywords: Cilnidipine, crystallo-co-agglomeration, DCM

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INTRODUCTION
For advancement in powder technology various new approaches are taken to design primary and secondary particles of pharmaceutical substances for several application like improvement in solubility, improvement in micromeritic and compression properties, obtain suitable polymorphs, modification of bioavailability.
Different techniques for enlargement of particle size are an important tool in modifying primary and secondary properties of pharmaceutical substance. There are many conventional processes which are used to enlarge the particle size and involve wider acceptability. But recently different non conventional techniques of particle size enlargement employed in pharmacy include extrusion spheronization, melt solidification, melt granulation, melt extrusion and spherical crystallization. Apart from modification in primary and secondary properties of particles, these techniques offer advantages in terms of reduction in the number of unit operations and processing cost. The suitability of these techniques depends on the desired properties of the enlarged particle and physicochemical properties of drug and excipients.
Particle size enlargement has become an important tool in modifying the flow properties & dissolution behaviors of pharmaceuticals. Literature survey reveals that particle size enlargement of drug is a widely used technique in industrial processing. It can be carried out by techniques such as melt extrusion, melt agglomeration, Crystallo –co agglomeration, ordered mixing and spherical crystallization

(Pawar A et al. 2004). Kawashima et al developed spherical crystallization technique. Spherical agglomeration technique has been developed to improve the wetting, micromeritic and mechanical properties of the drug. To overcome the limitation of spherical crystallization Kadam et al developed the CCA technique.(Kadam et al. 1997) Crystallo-co-agglomeration is an agglomeration process that transforms crystalline drugs directy into a compacted spherical form for improving the flowability, solubility and compactability by size enlargement of all, low dose, high dose, poorly compressible drugs and combination of drugs with or without diluents(Chaturvedi A et al. 2011)

Cilnidipine, a novel dihydropyridine Calcium channel blocker has been reported to exhibit excellent clinical effects on cardiovascular diseases. Cilnidipine is a yellow crystalline powder with poor water solubility. However the major drawback of cilnidipine is its poor dissolution and poor oral bioavailability and also poor flow property. The objective of the present work is to prepare crystallo-co-agglomerates of Cilnidipine with a view to improvement in its dissolution characteristics, improvement in its wettability, flow properties and mechanical properties, improvement in tableting behaviour of the drug by obtaining directly compressible agglomerates using various hydrophilic polymers. Physicochemical properties of raw cilnidipine and CCA contaning cilnidipine were characterized by FTIR, SEM, DSC, XRD, solubility study, dissolution study. The improvement in micromeritic properties were studied by Angle of repose, Hausner's ratio, Carr's index.

MATERIALS AND METHOD

Materials:

Cilnidipine was a kind gift from Laksh fine chem. Pvt Ltd, Anand. HPMC E5 LV, HPMC E15 LV, HPMC E50 LV were generously supplied by Colorcon Asia Ltd,Goa as gift samples. PEG 6000 gifted by Evonik Industries, Germany. PVP K-30 and PVP K-90 procured from ISP technologies.nic NJ. Poloxamer 188 and poloxamer 407 were gifted by BASF. PVA procured from Chemdye Corporation, Rajkot. All other chemicals and solvents used were of analytical grade(Allied chemical corporation, Vadodara). Distilled water was used throughout the experiment.

Methods:

Selection of solvent system

The solubility study of Cilnidipine was performed to select good solvents and poor solvents for the drug. Various solvents ranging from highly polar to nonpolar were tried for this study. About 2 ml of each solvent was taken and an excess quantity of the drug was added in it. These saturated solutions were then kept for 24 hours in orbital shaker at a temperature of 25 ± 1°C with constant shaking at 120 rpm (rpm: Revolutions per minute). The saturated solutions were then filtered and the concentration of drug in the solution was measured at 240 nm using an ultraviolet (UV)-visible spectrophotometer (Shimadzu, Japan). The solubility study was repeated three times in the same manner to obtain reproducible results (Garala K et al. 2012).

Preparation of crystallo-co-agglomerates

On the basis of the solubility data, good and poor solvents were identified and selected for preparing CCA of Cilnidipine. A crystallization protocol was designed in which the drug was dissolved in good solvent and this was poured into bad solvent dropwise, which was stirred using a four-blade mechanical stirrer. The stirring was continued for about 60 minutes at 1000rpm. The stirring was stopped when the overall mixture appeared clear at the top and the particles settled down. The agglomerates generated were filtered and dried at room temperature. Various polymers like PVP K 30, PVP K 90, HPMC, PEG 6000, PVA, Poloxamer etc., were screened to obtain crystallo-co-agglomerates of desired properties and desired dissolution behavior (Tapas et al. 2010).

Experimental Design:

After screening of polymers/stabilizers, a 3^2 full factorial design was used to optimize the concentration of poloxamer 407 and stirring speed was selected as two independent variables. Each variables at three level; experimental batches were performed at all nine possible combination. Experimental variables and their coded levels with actual values are given in table. All other factors were kept constant as mention in technique. The data was subjected to determine the effect of independent variables on dependant variable (dissolution behavior). A statistical model incorporating interactive and polynomial terms was used to calculate the response in order to optimized the formulation (Garala K et al. 2012).

Evaluation of Factorial Batches

Percentage yield:

The percentage yield of agglomerates was calculated by weighing the prepared agglomerates after drying stage as per the given

formula

$$\%Yield = \frac{Practical\ yield}{Theoratical\ yield} \times 100$$

Drug content:

Accurately weighed Crystallo-co-agglomerates (10mg) were dissolved in methanol in 10 ml volumetric flask. Appropriate dilutions were made with the same medium and the content was measured by UV spectrophotometer at 240 nm. The drug content was calculated using calibration equation.

Percentage drug dissolved in 150 min (C_{150}):

The dissolution rate studies of Crystallo-co-agglomerates (equivalent to 10 mg) were performed in triplicate in a dissolution apparatus using the paddle method (USP Type II). Dissolution studies were carried out using 900 ml of 0.4% SLS solution at 37 ± 0.5 °C at 75 rpm. The samples were withdrawn (5 ml) after 150 min and replaced with 5 ml of fresh media. The solutions were immediately filtered through a 0.45 µm membrane filter, suitably diluted and the concentrations of cilnidipine in samples were determined spectrophotometrically at 242.5 nm.

Evaluation of Optimized Batch

In-Vitro dissolution study of optimized batch and pure drug

The dissolution study of Crystallo-co-agglomerates of optimized batch and pure drug were performed in triplicate in a dissolution apparatus using the paddle method (USP Type II). Dissolution studies were carried out using 900 mL of 0.4% SLS solution at 37 ± 0.5 °C at 50 rpm. The samples were withdrawn (5 ml) at specific time interval 5, 10, 20, 30, 45, 60, 90, 120, 150 min and replaced with 5 ml of fresh media. The solutions were immediately filtered through a 0.45 µm membrane filter, suitably diluted and the concentrations of cilnidipine in samples were determined spectrophotometrically at 242.5 nm.

Scanning Electron Microscopy:

The morphology of CCA and Cilnidipine pure drug was investigated using scanning electron microscope (Make: FEG nano nova SEM 450) operated at an acceleration voltage of 5 kV. Samples were mounted on aluminium stubs with double sided adhesive carbon tape and then inserted into the chamber and low vacuum detector was used for the study.

Particle size analysis:

The particle size distribution of measurements of pure drug and crystallo-co agglomerates were performed using laser diffraction particle size analyser. Helium Neon (He Ne) laser beam was focused with minimum of 5 mW power using R3 fourier lens. Scattered light by particles is collected by fourier lens. The data was analysed by WINDOX software.

XRD study:

XRD study was performed to determine crystalline nature of agglomerates or changes in crystalline nature as compared to pure drug. The sample was irradiated with the monochromatized CuKα radiation and analysed between 2 to 50º θ.

Differential Scanning Calorimetry:

The DSC thermogram of optimized batch and pure drug was recorded by heating the sample at constant rate 10ºC/min over a temperature range of 45ºC to 220ºC.

Fourier transformed infrared spectroscopy:

A pellet of agglomerates and KBr (spectroscopic grade) and of pure drug was prepared using a hydraulic pellet press at pressure of 7-10 tonnes. FTIR was scanned from 4000-400 cm^{-1} using Perkin Elmer Spectrum GXFTIR, USA.

Determination of residual solvent limit:

Standard solvent for calibration was prepared by suitable dilution of the solvent used in preparation of crystallo-co-agglomerates. A weighed sample of agglomerates was placed into a small sample cup and was installed into the sample mounting unit. The residual solvent in the given sample was analysed by GC-HS. The term "Residual solvents" refers to compounds used in the manufacturing of pharmaceutical materials that may not be completely removed after processing. Solvents are labelled as class 1, class 2, and class 3 based on their suspected toxicity as per USP. Dichloromethane is a class 2 solvent and the residual specification limit is not more than 600 ppm.

RESULTS AND DISCUSSION

Selection of solvent system:

Saturation solubility study of Cilnidipine was done in different solvents like distilled water, Acetone, methanol, Ethanol, Dichloromethane (DCM), Dimethylsulfoxide(DMSO). The results of solubility studies are shown in figure 1.

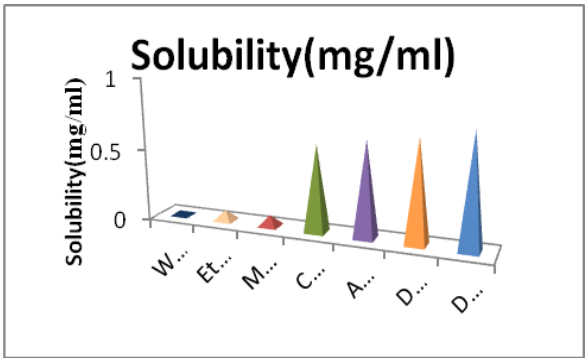

Figure 1: Solubility of Cilnidipine in Different Solvents

From the results of the above data Dichloromethane (DCM) was selected as good solvent as well as the Bridging Liquid and Distilled water was selected as a poor solvent. The bridging liquid should carry out preferential wetting of crystals and form liquid bridges during process of agglomeration. Simultaneously, the bridging liquid should be immiscible with bad solvent. Here bridging liquid is also acting as good solvent, it means it performs the dual role of acting as a good solvent and a bridging liquid.

Screening of polymers

Various hydrophilic polymers and their combinations were screened for preparation of crystallo-co-agglomerates. Saturation solubility studies of crystallo-co-agglomerates of Cilnidipine prepared using different polymers were done. The results are shown in table 1.

Sr no	Name of Polymer	Saturated solubility in water (mg/ml)			Solubility in water (mg/ml) (Mean±SD)
		I	II	III	
1	Pure Drug	0.000987	0.000946	0.000937	0.000957+0.0000266
2	HPMC E-50	0..050	0.0517	0.051	0.0509±0.000854
3	PEG 6000	0.00144	0.00148	0.00143	0.00145±0.000026
4	PVP K-30	0.00166	0.0015	0.00157	0.001577±0.0000802
5	PVP K-90	0.07075	0.070	0.0687	0.069817±0.001037
6	PVP K-30:PVP K-90(1:1)	0.017	0.020	0.021	0.01933±0.002081
7	**HPMC E-5:E-15:E:50(1:1:1)**	**0.098**	**0.104**	**0.115**	**0.1056±0.0000208**
8	**PVP K-30:PVP K-90(1:2)**	**0.087**	**0.093**	**0.084**	**0.088±0.004582**
9	PVP K-30:PVP K-90(2:1)	0.01742	0.01687	0.0167	0.01699±0.0003764
10	**Poloxamer 407**	**0.248**	**0.230**	**0.239**	**0.239±0.009**

Table 1: Saturated solubility study of Crystallo-co-agglomerates using different polymers as stabilizers

Aqueous solubility of crystallo-co-agglomerates improved as compared to pure drug. This may be due to change in crystal forms because of different habit, structure and surface modification and in some instances solvents induced into the crystal forms. Solvets or clathrates that change the surface properties and the reactivity of drug particles and the internal energy of the molecules, playing important role in increasing solubility. The CCA prepared by incorporating hydrophilic polymers showed increase wettability of agglomerates resulting in improved aqueous solubility**.** From the results of above data Polyvinylpyrrolidone [PVP K-30:PVPK-90 (1:2)], Hydroxy propyl methyl cellulose [HPMC E-5:HPMC E-15:HPMC E-50 (1:1:1)] and Poloxamer 407 produced Crystallo-co-agglomerates of desired characteristics. From above result poloxamer 407 gave maximum dissolution than other polymer so for further study poloxamer 407 was selected.

Characterization of factorial batches:

Drug content, % yield, and percentage drug dissolved in 150 min (C_{150}), Angle of repose, Carr's index, Hausner's ratio was calculated. Table 2 represents data for drug content and % yield, micromeritic properties of factorial batches. Figure 2 represents the data for percentage drug dissolved in 150 min (C_{150}).

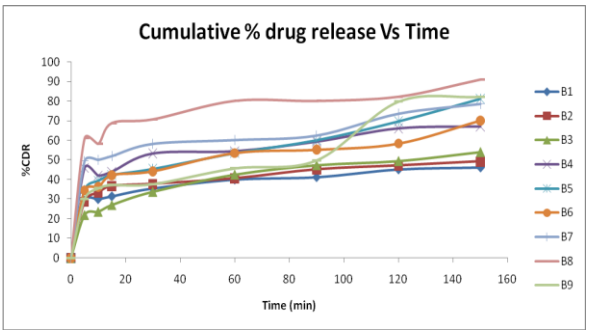

Figure 2: Dissolution profile of factorial batches

From the dissolution profile of factorial batches, B-8 batch showed maximum 91.12% drug release in 150 min in 0.4% SLS solution.

Statistical analysis

The statistical optimization procedure was performed with the help of optimization software Design expert 8.0.7.1. The software performs the multiple regression analysis (MRA), analysis of variance (ANOVA) and statistical optimization.

Multiple regression analysis of factorial design results:

The use of regression analysis in 3^2 factorial designs generates polynomial equations for different models, with interacting terms and regression coefficients, useful in evaluating the responses. The software generates two models, particularly, full model (non-significant terms included) and reduced model (excluding non-significant terms). In the full model study, the responses were analyzed using the quadratic equation below:

$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22}$

Where,

Y = Selected response
X_1 = Concentration of poloxamer 407
X_2 = Speed of stirring
b_0= Intercept (arithmetic mean response of 9 runs)
b_1, b_2, b_{12}, b_{11}, b_{22} = Coefficient computed from the response of the formulation in design

Batch No	Drug content	%Yield (%w/w)	Angle of Repose	Carr's Index	Hausner's Ratio
B-1	83.14	66	27±0.5372	4.761±0.076	1.05±0.08
B-2	91.40	85.33	28.23±1.2057	4.545±0.1	1.047±0.057
B-3	83.25	65.33	30.46±1.009	4.761±0.076	1.050±0.23
B-4	79.95	73	32±1.005	10±2.645	1.11±0.23
B-5	77.09	75	30.65±1.476	9.090±0.854	1.10±0.11
B-6	93.61	66	31.41±0.504	4.761±0.076	1.05±0.086
B-7	87.99	64	28.270±0.4100	5±1	1.052±0.086
B-8	**82.04**	**74**	**25.20±0.592**	**6.25±1.56**	**1.066±0.115**
B-9	88.10	70	25.36±0.591	4.347±0.51	0.045±8.5 E-18

Table 2: Drug content and % yield of factorial batches

Regression equation(Full Model)	**$R1 = +77.92+17.03X_1+2.40X_2-1.14X_1X_2-5.99X_1^2-7.56X_2^2$**				
Coefficient(b_0)	77.92				
Correlation coefficient	0.9634				
Adjusted R-squared	0.9025				
Predicted R-squared	0.6162				
Adequate precision	11.091				
	b_1	b_2	b_{12}	b_{11}	b_{22}
X coefficients	+17.03	+2.40	-1.14	-5.99	-7.56
p Value	0.0036	0.3241	0.6797	0.1880	0.1212

Table 3: Results obtained of C_{150} from factorial batches

p value of b_1 (for factor X_1) is <0.005(significant) and also it has the positive sign, Hence concentration of polymer ($X_{1)}$ play a very important role on characteristics of CCA.

Final equation in terms of coded factor is:

$R1 = + 77.92 + 17.03X_1 + 2.40X_2 - 1.14X_1X_2 - 5.99X_1^2 - 7.56X_2^2$

The value and sign of regression coefficient (b) indicates the magnitude of influence of the particular term on the response. The regression coefficients give the average change in a response when the particular factor is changed by a unit, when all the other terms remain constant. A positive sign on the regression coefficient indicates the factor has a positive effect on the response and negative sign indicates a negative effect. Data for multiple regression analysis is shown in table 3.

Construction of contour plot and surface plot:

From the contour plot figure 3, we can say that as the level of variable X_1 – (concentration of poloxamer) increases from 0 to +1, C_{150} value increases. At the high level of variable X_1(level +1) maximum rate of dissolution is observed. In the contour plot maximum value of C_{150} (around 91%) is shown by red coloured area, while area with blue colour shows minimum value of C_{150} (around 50%). As the value of variable X_2 (Speed of stirring) increases from -1 to 0 level, C_{150} value increases, but variable X_2(Speed of stirring) from 0 to +1 C_{150} value decreases. From the contour plot we can say that at the high level of Variable X_1(A) and at medium level of variable X_2 (B) maximum value of C_{150} (around 91%) is obtained. Concentration of poloxamer has effect on rate of dissolution, at lower concentration of poloxamer C_{150} value is less, at high level C_{150} value is maximum. Variable X_2 also has effect on rate of dissolution. When agitation speed was at low level(500rpm) large irregular agglomerates were obtained, where the shear energy may not be sufficient for formation of spherical shape of agglomerated crystals. Agglomerates at medium level(1000rpm) speed resuts in uniform size distribution. It appears to be clear that the optimum shear force of the agitated liquid and collisions with equipment surfaces and other particles were squeezing and molding the irregular agglomerates into the most perfect spherical shape while at high level(1500rpm) the agglomerated crystals were with randomly broken edges due to high force of agitation**.** From the above facts we can conclude that High level of poloxamer concentration and medium level of speed gives maximum value of C_{150}(around 91%) .

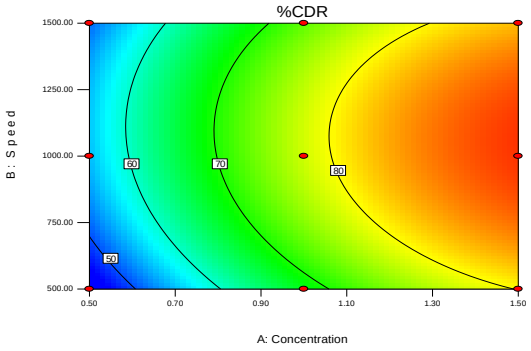

Figure 3: contour plot

3D response surface plot:

figure 4 shows 3D response surface plot for C_{150} (%CDR). From 3D response surface plot we can check the effect of variables on response. From the graph we can say that maximum C_{150} (%CDR) value is obtained at high level (+1 level) of variable X_1 (A) and medium level (0 level) of variable X_2(B). Region with red colour shows maximum value of C_{150} (%CDR) while the region with blue colour and green colour shows minimum and intermediate value of C_{150} (%CDR) respectively.

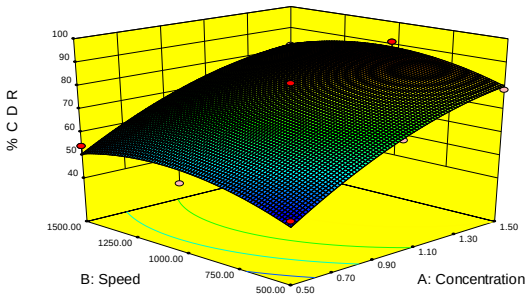

Figure 4: Surface response plot

Optimization of formula

In the light of above facts, two variables were optimized. At high level of X_1 and medium level of X_2 % CDR is maximum(91%). The optimized formula given in table 4.

Coded value		Actual value	
X_1	X_2	X_1	X_2
+1	0	1.5% w/v poloxamer soution	1000

Table 4: Formula for optimized batch

Evaluation of check point batches

Two checkpoint batches CK-1 and CK-2 were prepared to confirm the validity of contour plot and the equation generated by multiple

regression analysis. Result shown in table 5.

Batch no	Predicted value of C_{150}(%CDR)	Experimental value of C_{150}(%CDR)	% Relative error
CK-1	83.96	81.5	2.92
CK-2	64.53	62.8	2.68

Table 5: Comparison of experimental value with predicted value

Here % relative error was found to be less than 5%. It indicates that there is less difference between experimental value of response and predicted value of response calculated by software. This confirms the validity of model and model equations.

Evaluation of optimized batch

In-vitro dissolution study of pure drug and optimized batch of agglomerates:

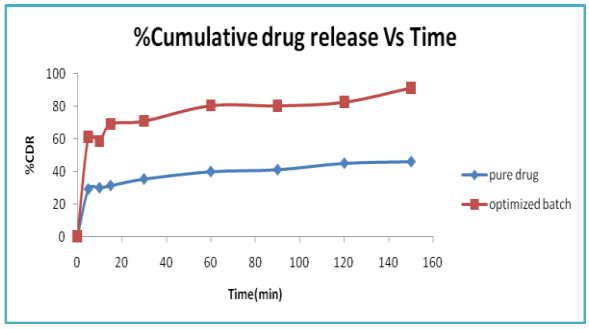

Figure 5: Dissolution profile of optimized batch

From dissolution profile of optimized batch we can conclude that there is improvement in rate of dissolution of Crystallo-co-agglomerates as compared to pure drug cilnidipine. Agglomerates showed 91.124 % drug release in 150 min while pure drug showed 46.128% drug release in 150 min. Improvement in rate of dissolution of agglomerates may be attributed to changes in crystallinity of drug and improved wettability of Crystallo-co-agglomerates**.**

Scanning electron microscopy:

Figure 6 represents the results of SEM. From the images we can conclude that pure drug-Cilnidipine crystals exhibited plate like irregularly shaped crystals which are responsible for its poor flow property. Surface morphology of Crystallo-co-agglomerates showed that the agglomerates were formed by various small crystals which were closely compacted into nearly spherical form. All the agglomerates were nearly spherical in shape which improved their flow property and rate of dissolution.

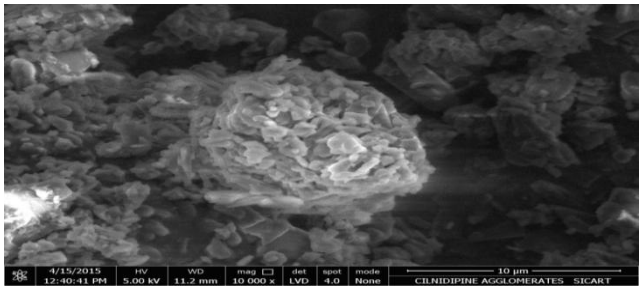

Figure 6(a): SEM of Crystallo-co-agglomerates of optimized batch

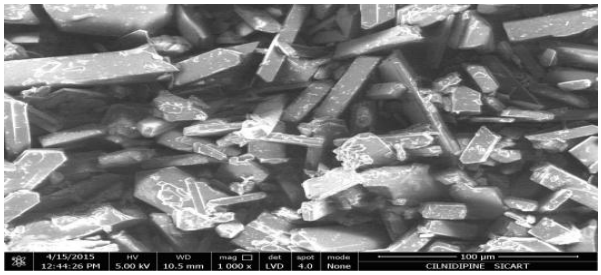

Figure 6(b): SEM of Pure drug

Particle size analysis:

Result of particle size analysis of pure drug and Crystallo-co-agglomerates is shown in table 7 .From the result we can conclude that there is increase in size of agglomerates as compared to pure drug. The agglomerates have shape factor 1.

Cilnidipine		Crystallo-co-agglomerates	
X10	**X99**	**X10**	**X99**
1.97µm	54.42µm	1.80	340.95 µm

Table 6: Particle size analysis of pure drug and Crystallo-co-agglomerates

XRD study:

XRD spectra of pure drug and Crystallo-co-agglomerates are shown in figure 7 XRD spectra of pure drug showed sharp diffraction peaks which indicate crystalline nature of the drug. In case of Crystallo-co-agglomerates changes in the intensity and height of peaks was observed. XRD spectra of agglomerates showed certain new peaks while certain peaks were disappeared which were present in XRD spectra of pure drug, this confirms the changes in crystallinity of pure drug.

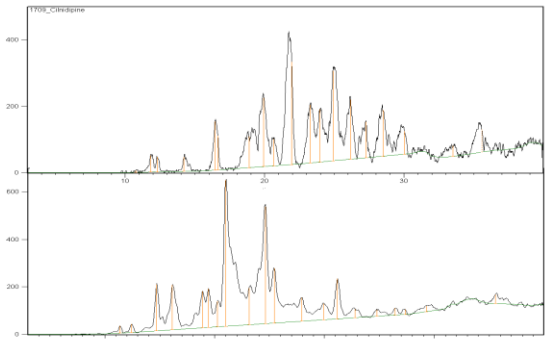

Figure 7: XRD spectra of pure drug Cilnidipine and crystallo-co-agglomerates of optimized batch

Differential scanning calorimetry:

Results of DSC of pure drug and Crystallo-co-agglomerates are shown in figure 8. Data for the same are shown in table 7.

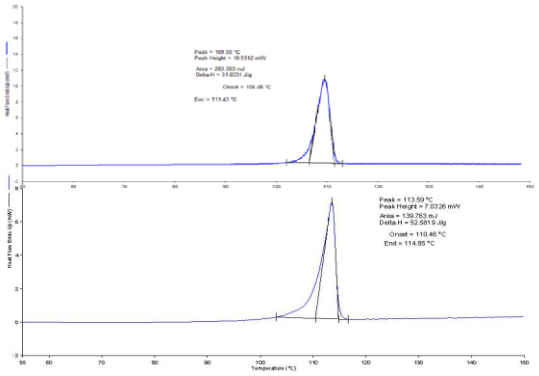

Figure 8: DSC thermogram of pure drug and crystallo-co-agglomerates of optimized batch

Sample	Melting point(ºC)	ΔH value(J/g)
Cilnidipine (pure drug)	109.58	81.0331
Crystallo-co-agglomerates	113.59	52.5819

Table 7: DSC data of pure drug and Crystallo-co-agglomerates

From the above data we can conclude that there is slight change in melting point of agglomerates as compared to pure drug, also there is reduction in ΔH value of Crystallo-co-agglomerates as compared to pure drug which confirms the changes or reduction in the crystallinity in crystallo-co-agglomerates**.**

Fourier transformed infrared spectroscopy:

Results of FTIR of drug, drug-polymer and Crystallo-co-agglomerates are shown in figure 9. By comparing the FTIR spectrum of Drug and Crystallo-co-agglomerates we can conclude that all the characteristic absorption peaks were retained which confirms drug-polymer compatibility. FTIR spectrum of CCA showed there no changes occurred in chemical structure and did not present a great fingerprint difference**.**

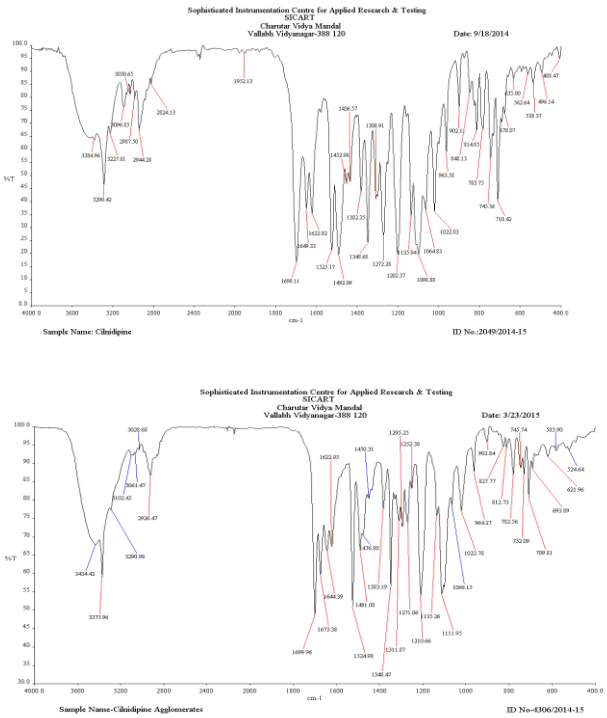

Figure 9: FTIR spectra of pure drug and crystallo-co-agglomerates of optimized batch

Determination of residual solvent limit:

Dichloromethane is a class 2 solvent. To determine its traces in the optimized batch GC with Head space was done. Standard DCM solution of 1000 ppm was used for comparison with the test solution. Retention time of standard solution is 1.24 s. Peak at this time was observed in the graph of test solution (optimized batch). From the area of standard and test solution the concentration of DCM in optimized batch was calculated and it was found to be 0.869 ppm which is within the specification limit**.**

CONCLUSION

Crystallo-co-agglomerates of Cilnidipne prepared using poloxamer 407 (1.5%W/V-external phase) showed improvement in rate of dissolution and micromeritic properties as compared to pure drug. Increase in the dissolution rate of agglomerates may be due to the deposition of hydrophilic polymer on the recrystallized drug surface and better wettability of spherical agglomerates. Improvement in the rate of dissolution of agglomerates may also be due to changes in the crystal forms, crystal habit and surface modification. Improvement in flow properties as compared to pure drug. The reason for the excellent flowability of spherical crystals is the significant reduction in the interparticle friction because of perfect spherical shape and

the larger size of the crystal. XRD and DSC study confirmed the changes in crystallinity of drug. The crystallo-co-agglomerates improve compressibility, and compaction properties. The crystallo-co-agglomerates are directly compressible and can be formulated into a tablet.

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