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FORMULATION AND EVALUATION OF SPHERICAL CRYSTAL AGGLOMERATES OF NISOLDIPINE

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ABSTRACT

Utilization of herbs for medicinal purpose started in the early history of mankind several thousand years The aim of the present study was to prepare and characterize the spherical crystal agglomerates ofnisoldipine with different polymers like PEG 4000, PEG 6000, PVP and PVP K30 byusing Quassi emulsification solvent diffusion technique for enhancement of solubility, flowability, packability of nisoldipine.All the prepared agglomerates were evaluated for their flow behaviour, packability and solubility. The prepared spherical crystal agglomerates exhibited excellent physicochemical properties like solubility, flowability, packability compared with the pure nisoldipine. Agglomerates AG15 showed the better solubility and drug release in comparison of pure drug. The agglomerates AG15 was further characterized by using SEM, X-Ray diffractometry and differential scanning calorimetry. SEM studies showed that the crystal possesses a good spherical shape with smooth and regular surface.DSC thermo grams showed the changes in the melting peak of the nisoldipine in spherical crystal agglomerates suggesting the change in crystallinity of nisoldipine.The XRD revealed a characteristic decrease in the crystallinity of the nisoldipine.These results show that partial amorphization of drug leads to enhancement of drug solubility and dissolution rate.

Keywords: Spherical crystal agglomarates, Quassi emulsification solvent diffusion technique, Nisoldipine, Solubility, packability.

INTRODUCTION:

The quality of a solid pharmaceutical preparation is influenced by primary micromeritic characteristics such as the shape and size of drug crystals, especially when large amounts of poorly soluble drugs are formulated. To improve the dissolution rate of poorly soluble drugs, fine crystals are preferred over large crystals because they provide a greater surface area. Now days, the most importance is given to enhance the dissolution rate of the poorly soluble drugs, so, it increases the bioavailability of drug [1].

However, micronization can change drug powder properties such as wettability, compressibility, packability and flowability and thus prevent efficient powder packaging [2]. This technique involves selective formation of agglomerates of crystals which could be easily compounded with other pharmaceutical powders due to their spherical shape [3].

Spherical crystallization is carried out by different methods such as spherical agglomeration method, quasi-emulsion solvent diffusion system (QESDS), ammonia diffusion system and Neutralization technique. Out of these techniques, the QESDS is most commonly used [4]. Using this method, spherical crystallization can be carried out by using a mixed system of three partially miscible solvents, i.e. good solvent-bridging liquid-poor solvent [4].

Nisoldipine, an anti-hypertensive agent has poor flow properties and compressibility. It is a yellow crystalline powder. It has limited aqueous solubility as well as lower dissolution rate, which is absorbed slowly after oral administration and thus requires higer dose.

To overcome the limitations associated with solubility, dissolution, flowability and compressibility, the spherically agglomerated crystals of nisoldipine were prepared in the present investigation[5].

MATERIALS AND METHODS

Nisoldipine was obtained as a gift sample from long Xintong Technology Co. Ltd. Su Zhou (china). Different grades of Polyethylene glycol and PVP were obtained from Sigma Aldrich Mumbai (India). Dichloromethane and chloroform were obtained from Loba Chemie, Mumbai. All other chemical used were of analytical grades.

Preparation of Nisoldipine agglomerates by quassi emulsion solvent diffusion technique:

Nisoldipine (2.5 g) was dissolved in the mixture of 5 ml of acetone and 1 ml of dichloromethane thermally controlled at 40°C so as to form the saturated solution of the drug. The solution was poured into 100 ml of distilled water with a stirring rate of 800 ± 40 rpm using a propeller type of agitator at room temperature. After agitating the system for 30 min, the prepared agglomerates were collected by filtration through Whatman filter. The spherical crystals were placed at 45°C for drying in a hot air oven for 2hrs and then stored in desiccators [6].

Table 1: Preparation of Nisoldipine agglomerates

Ingredients (mg)	Nis: PEG 4000	Nis:PEG6000	Nis: PVP	Nis: PVP K30	Nis:PEG4000 + PEG6000	Acetone (ml)	DCM (ml)	Water (ml)
AG1	1:0.5	-	-	-	-	5	1	100
AG2	1:0.75	-	-	-	-	5	1	100
AG3	1:1	-	-	-	-	5	1	100
AG4	-	1:0.5	-	-	-	5	1	100
AG5	-	1:0.75	-	-	-	5	1	100
AG6	-	1:1	-	-	-	5	1	100
AG7	-	-	1:0.5	-	-	5	1	100

AG8	-	-	1:0.75	-	-	5	1	100
AG9	-	-	1:1	-	-	5	1	100
AG10	-	-	-	1:0.5	-	5	1	100
AG11	-	-	-	1:0.75	-	5	1	100
AG12	-	-	-	1:1	-	5	1	100
AG13	-	-	-	-	1:0.5	5	1	100
AG14	-	-	-	-	1:0.75	5	1	100
AG15	-	-	-	-	1:1	5	1	100

Evaluation of Spherical Crystal Agglomerates

All the prepared agglomerates were evaluated for flow properties like bulk density[7], tapped density[8], Carr's index,[9] Hausner's ratio[10] and angle of repose[11].

Kawakita equations: Packability and compactibility parameters like ***a*** (compressibility), ***b*** (cohesiveness) were determined by Kawakita equation. The values of '**a**' and '**b**' were computed from the slope and intercept obtained from the linear plot of n/C Vs n.

Kawakita Equation: n/C = 1/(ab) + n/a

Where, C = (*V0* – *Vn*)/V0; *n* is number of tapping; *V0* is initial volume and *Vn* is volume after n no. of tap; *a, b* is the constants representing packability and compactibility of powder under mechanical force.[12]

% ProductionYield: The spherical crystal agglomerates were weighed and the percentage yield was calculated using theequation.[13]

$$\% \text{ Yield} = \left(\frac{\text{Practical yield}}{\text{theoratical yield}}\right) X\ 100$$

Drug Content: For determination of drug content the Spherical agglomerates of nisoldipine equivalent to 100 mg of nisoldipine was triturate and dissolved in methanol. Appropriately diluted sample was filtered and drug content was determined spectrophotometrically at 238 nm using UV- visible spectrophotometer.[14]

Partical size: Prepared spherical agglomerates were observed under optical microscopy for size and of spherical crystal agglomerates.

Saturation Solubility: agglomerates equivalent to 10 mg of nisoldipine was accurately weighed and transferred in to 50 ml beaker and 10 ml of distilled water was added. The content was kept for stirring

on shaker for 24 hr at room temperature. Present amount of drug was estimated by using UV spectrophotometer at 238 nm.[15]

In Vitro Dissolution Studies: The dissolution rates of agglomerates was measured using the USP dissolution apparatus type I. In vitro Dissolution Test was carried out by using 900 ml of 0.1 N HCl+ 0.5% SLS. The temperature of dissolution medium was maintained 37± 0.5 °C and Basket was rotated at 50 rpm. The aliquots of 5 ml were filter and was withdrawn at regular time intervals and filtered , analyzed by UV visible spectrophotometer.[16]

Characterization of spherical crystal agglomerates:

Differential scanning calorimetry

Sample, approximately weighted was scaled in Aluminum DSC test pans. Each sample was run against a reference pan of air in stander mode under a nitrogen atmosphere. Measurement was performed at the temperature range 145^0C -155^0C for Nisoldipine. The thermal properties were determined form the resulting DSC thermographs.

Scanning Electron Microscopy

SEM which used to produces image of sample by scanning the surface with focused beam of electrons. Interaction tack place between electrons and atoms, which produces various single that contain in formulation about sample surface topography and composition. Morphological evaluation of drug loaded agglomerates was carried out using Joel Scanning Electron Microscope with Oxford EDS system.

X-ray Diffraction

In XRD, sample has been passed into sample holder, have smooth surface and hold in sample at an angle of 450. For XRD crystalline powder is ideal but solid samples small volume of sample can also be used but will have varying degree of effectiveness. The more crystalline the sample, the better result will be. For Characterization of crystalline state, the Powder X-ray diffraction studies were carried out by using X'pertPRO X-ray Diffractometer at SVNIT Surat. The Nisoldipine and agglomerates was ground into powders with a mortar and pestle and the cross section of samples was exposed to X-ray radiation. The scanning angle ranged from 00 to 500 of 2θ.

Results and discussion:

Table no:1 Flow behaviour of batches AG1-AG15

Formula code	Bulk density (gm/cm^3) ±SD n=3	Tapped density (gm/cm^3)±SD n=3	Carr's Index (%)±SD n=3	Hausner's Ratio ±SD n=3	Angle of Repose (θ)±SD n=3	Kawa –kita constants	
						a	b
Pure Drug	0.05 ± 0.02	0.07 ± 0.03	28.5± 0.05	1.4± 0.07	42θ± 0.04	0.621	0.019
AG1	0.42± 0.02	0.49± 0.04	14.29± 0.04	1.17± 0.04	20.12±2.40	0.502	0.020
AG2	0.45± 0.04	0.51± 0.05	11.76± 0.06	1.13± 0.07	28.12±1.26	0.535	0.021
AG3	0.43± 0.05	0.53± 0.03	18.87± 0.02	1.23± 0.08	32.24±1.73	0.548	0.022
AG4	0.48± 0.02	0.56± 0.03	14.29± 0.04	1.17± 0.05	21.10±1.80	0.482	0.023
AG5	0.48± 0.03	0.55± 0.05	12.73± 0.05	1.15± 0.06	27.12±2.30	0.475	0.024
AG6	0.48± 0.05	0.54± 0.04	11.11± 0.08	1.13± 0.04	24.55±1.20	0.429	0.025
AG7	0.46± 0.04	0.50 ± 0.06	08.00± 0.07	1.09± 0.08	20.23±0.96	0.459	0.026
AG8	0.43± 0.06	0.49± 0.04	12.24± 0.05	1.14± 0.02	29.89±1.78	0.446	0.024
AG9	0.46± 0.05	0.52± 0.04	11.54± 0.04	1.13± 0.06	26.75±1.76	0.552	0.028
AG10	0.54 ± 0.05	0.65 ± 0.04	10.9 ± 0.5	1.20± 0.05	32.20±2.30	0.546	0.026
AG11	0.53 ± 0.05	0.65 ± 0.06	11.6 ± 0.2	1.21± 0.05	25.82±1.20	0.589	0.027
AG12	0.52 ± 0.04	0.66 ± 0.05	13.9 ± 0.1	1.26± 0.04	23.12±0.96	0.439	0.028
AG13	0.54 ± 0.04	0.66 ± 0.06	12.7 ± 0.3	1.23± 0.01	21.26±1.78	0.479	0.027
AG15	0.54 ± 0.06	0.65 ± 0.04	10.8 ± 0.4	1.19± 0.04	20.12±2.30	0.425	0.029

Table no: 2 Evaluations of batches AG1-AG15

Formulation	Drug content±SD n=3	Production Yield(%)±SD n=3	Particle size(um)±SD n=3	Saturation Solubility(mg/ml)±SD n=3
AG 1	94.12±1.89	85.52±1.25	431.54±2.48	35.62±0.56
AG 2	95.86±2.48	84.67±2.35	324.34±4.89	31.34±0.89
AG 3	96.58±1.68	83.76±1.98	496.41±3.48	38.76±0.67
AG 4	96.52±2.85	82.35±2.69	214.25±2.68	35.25±0.88
AG 5	95.23±1.68	82.62±2.24	354.60±4.59	32.68±0.98
AG 6	95.89±2.45	84.56±1.35	456.31±1.97	34.81±0.76
AG 7	93.54±1.95	85.34±2.04	463.16±2.67	26.85±0.56
AG 8	94.46±1.64	84.87±2.38	345.26±5.72	29.25±0.64
AG 9	95.23±2.47	81.56±1.45	265.61±4.82	24.64±0.64
AG 10	95.56±1.73	83.25±2.76	459.65±2.03	31.67±0.82
AG 11	94.87±2.56	82.63±1.21	484.85±1.89	33.78±0.94
AG 12	95.68±1.72	82.54±2.48	498.54±5.59	29.23±0.53
AG 13	97.65±2.37	90.57±1.19	489.72±3.41	45.22±0.88
AG 14	97.52±2.64	90.46±2.46	503.81±6.32	43.97±0.92
AG 15	98.34±1.78	90.59±1.64	510.94±4.57	47.56±0.81

In vitro Drug study:

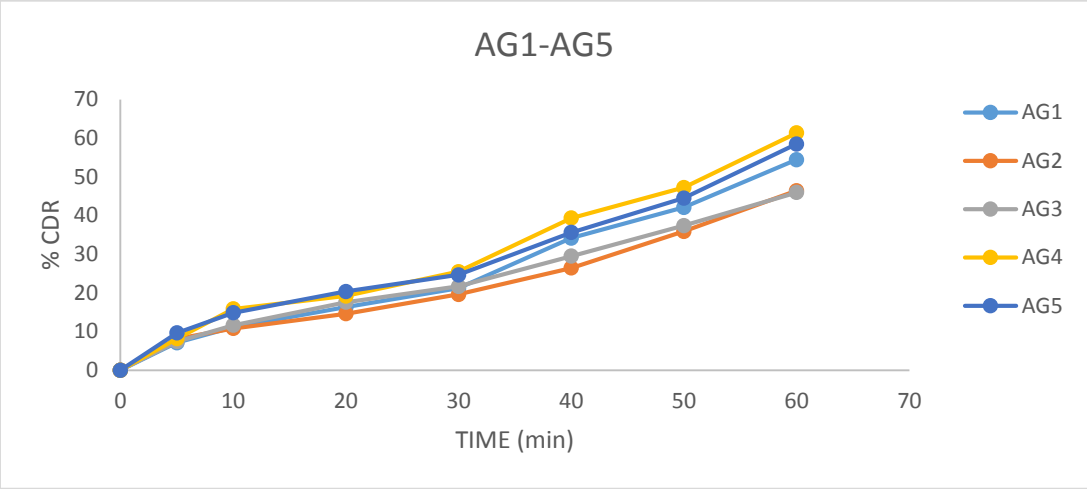

Figure. 1: In Vitrodrug release of batches AG1-AG5

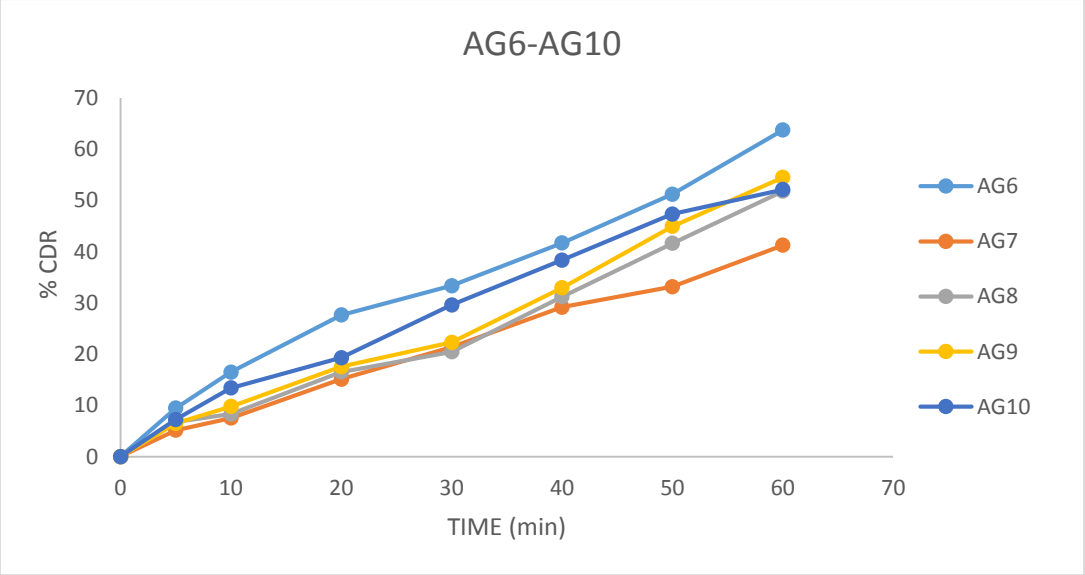

Figure 2: In Vitrodrug release of batches AG6-AG10

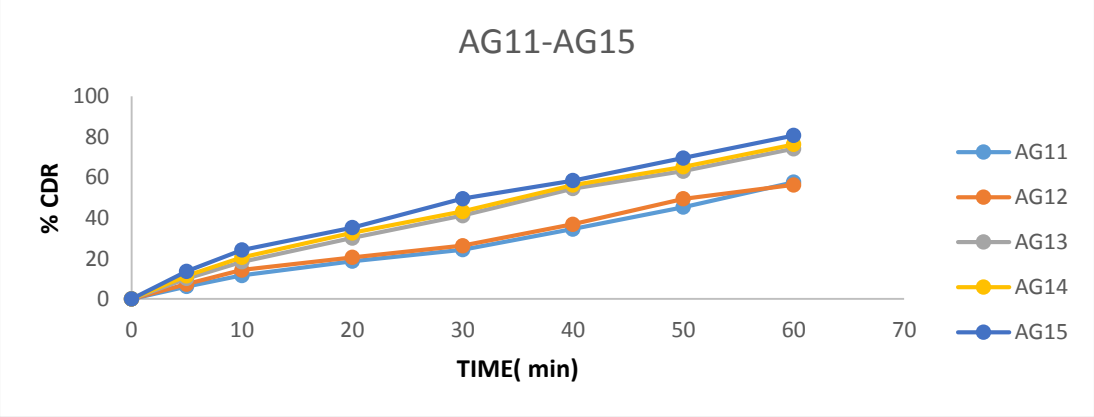

Figure 3: In Vitrodrug release of batches AG11-AG15

The in-vitro drug releases of agglomerates were found to 56.35%, 63.74%, and 61.35%. AG 15 containing PEG 4000+PEG 6000 in the ratio of 1:1 shows maximum release (80.17) at 60 minutes.so the mixture of PEG 4000 and PEG 6000 shows maximum Solubility than compare to other polymers.

Characterization of spherical crystal agglomerates:

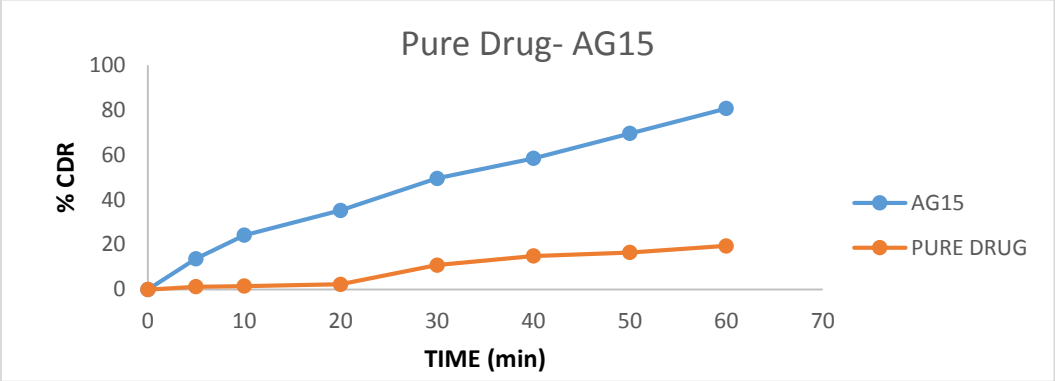

Figure 4: In vitrodrug release of pure drug and AG15

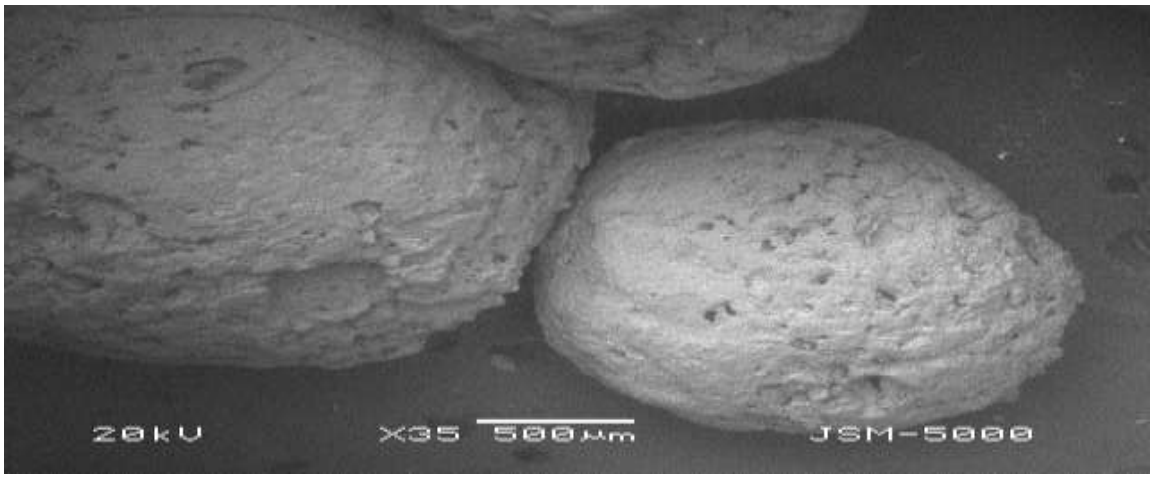

Figure 5: SEM of batch AG15

Figure : 5 SEM images showed that spherical agglomerates prepared by quasi emulsion solvent diffusion method were finely spherical and uniform.

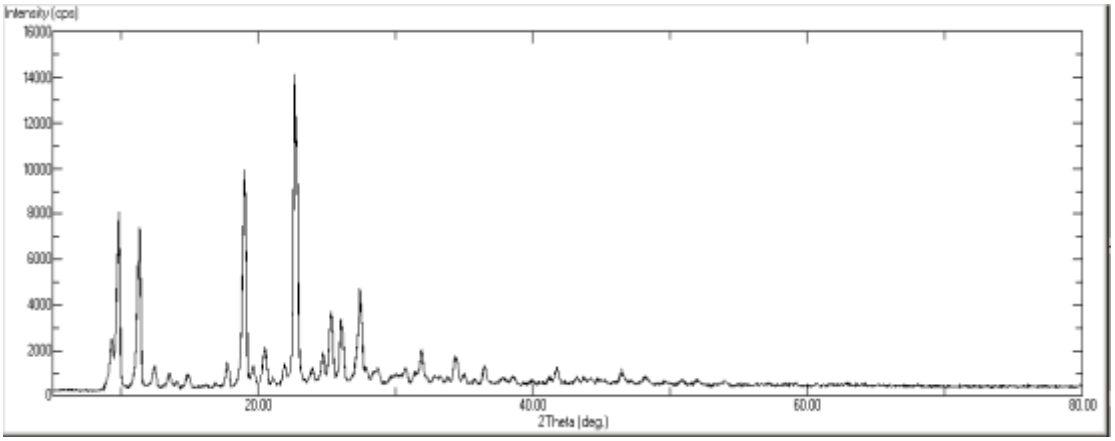

Figure 6: X-ray diffraction pattern of Nisoldipine

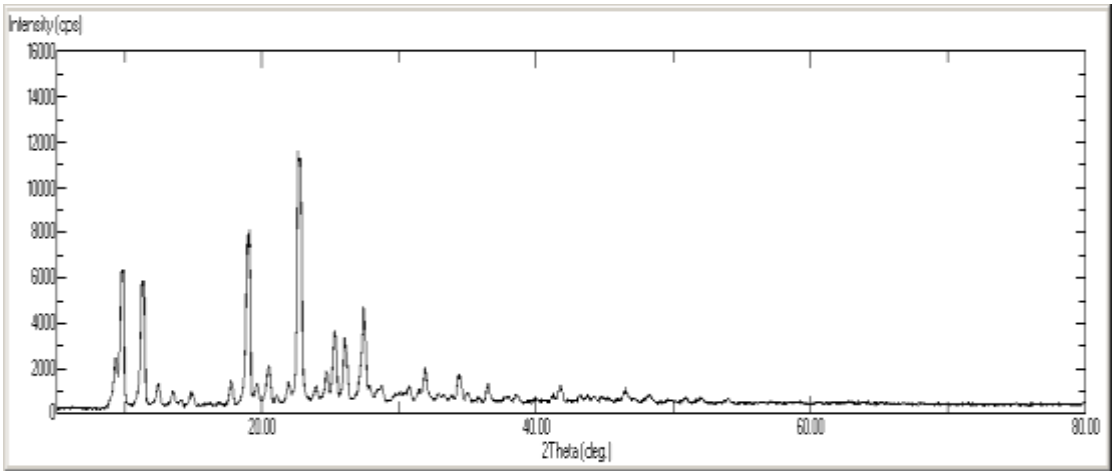

Figure 7: X-ray diffraction pattern of batch AG15

X-ray Diffraction of drug, and spherical crystal Agglomerates shows X-ray diffractogram of pure drug showing peaks appearing at 9.720, 11.210, 12.380, 18.950, 22.660, 25.240,27.400, 44.430 at 2θvalues supporting crystalline nature of drug while fiX-ray Diffraction of Nisoldipine agglomerates shows absence of characteristic peaks of nisoldipine which indication that the drug has almost converted from crystalline to amorphous state. Thus, these studies confirm that conversion of drug from its crystalline to amorphous state which result in solubility enhancement of drug. The strongly bound crystalline lattice structure was replaced by the nearly bound random structure of amorphous drug.

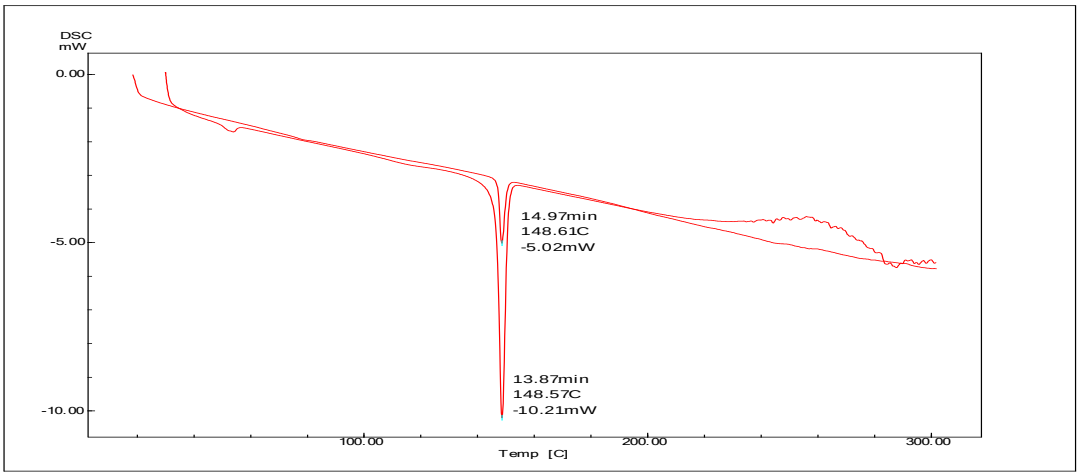

Figure8: Overlay DSC of Nisoldipine and best batch AG15

The DSC thermogram of pure drug and crystal agglomerates shows a characteristic endothermic peak at 148.61^{0}C which reflect its melting point and the sharp peak indicating that the Nisoldipine was in crystalline state. In figure no: 8 DSC thermogram of Nisoldipine Agglomerates shows absence of characteristics endothermic peak at 148.57 ^{0}C which indicates that nisoldipine was completely transformed into amorphous form.

Conclusion:

From the above observations, it was conclude that agglomerated crystals of Nisoldipine with different polymers like PEG4000, PEG 6000, PVP, PVP K30 were prepared by the Quassi Emulsion Solvent Diffusion technique showed an improvement in the solubility, dissolution rate, packability and flowability. AG15was found to be a best batch in solubility and dissolution enhancement of Nisoldipine from agglomerates.

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