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RESEARCH ARTICLE

PREPARATION AND CHARACTERIZATION OF SPHERICAL AGGLOMERATES OF LANSOPRAZOLE

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ABSTRACT

General methods of spherical crystallization are spherical agglomeration, quasi emulsion solvent diffusion and ammonia diffusion method. In this study directly compressible tablets of Lansoprazole form spherical crystallization were effectively prepared with improved physico-chemical properties. Agglomerates were prepared by emulsion solvent diffusion method using methanol, chloroform and phosphate buffer pH 6.8 as good solvent, bridging liquid and poor solvent respectively. Spherical crystals characterized by PXRD, DSC, SEM, FTIR, and in- vitro drug release. Tablet from agglomerates were prepared by mixing with excipients and compressed by rotary tablet machine. Evaluation parameters like weight variation, hardness of the tablet, friability, thickness, disintegration test, drug content uniformity and in vitro release studies were performed. PXRD, DSC and FTIR data shows that no any interaction between drug and polymer. The spherical crystals show good dissolution profile. SEM image shows that spherical crystals of Lansoprazole are spherical in shape. The water solubility of spherical crystals of Lansoprazole was increased as compared with pure drug. Spherical crystallization is having wide applications in pharmaceuticals like to increase the bioavailability of drugs that have poor aqueous solubility is a great challenge to formulate solid dosage form The spherical crystallization method is simple and easy at lab level; this approach should have a general applicability for many poorly water-soluble drugentities.

KEY WORDS: Spherical Crystallization, Solubility, Flowability, Compactability, Bioavailability.

INTRODUCTION

In the field of powder technology attempts are undertaken to design primary and secondary particles of pharmaceutical substances for various applications, such as improvement in solubility, obtaining suitable polymorph, improvement in micrometrics and compression properties, and modification of bioavailability[1][2] Spherical crystallization is a nonconventional particle-size enlargement technique that involves crystallization and agglomeration using bridging liquid[3][4]. Different methods have been reported to achieve super saturation during spherical crystallization[5][6].Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. From the manufacturing point of view tablets can be produced at much higher rate than any other dosage form. Tablet is the moststable readily portable and consumed dosage form. The formulation of tablet is optimized to achieve goals. The focus today in the business is better drug delivery concepts, but also makes the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products. These have been renewed interest in examining the potential of direct compression Tabletting over recent years since in comparison to the used at the more traditional granulation

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process. Such manufacturing of the tablets involves simple mixing and compression of powders which gives benefits like time andcost saving [8].Thus direct Tabletting technique has been widely usedsuccessfully for various drugs. But it strongly depends upon the quality of the crystals used.Crystals can be modified by recrystallizing the drug in different ways, which affect physical and physic chemical properties such as melting point, solubility, true density, dissolution profile.Recrystallization method is simple and inexpensive enough for scaling up to commercial level. Itreduces time and cost by enabling faster operation, less machinery and fewer personnel. It gives important advances in the different pharmaceutical dosage form technology [9] A crystal is defined as a homogenous particle of solid which is formed by solidification underfavorable conditions, of a chemical element or a compound, arranged at definite angles to oneanother in definite geometric form. In other words, a crystalIs one in which the internal atomic ormolecular arrangement is regular and periodic in three dimensions over intervals which are largecompared with unit of periodicity. The smallest arrangement of atoms and molecules whichrepeats regularly and is a true representation of crystal structure is known as “Unit Cell”. Crystallattice is defined as a three dimensional network of imaginary lines connecting the atoms. Thedistance between the centers of two atoms is called as the length of unit cell and angle betweenthe edges of a “unit cell” is called lattice angle[10].Crystals could be generated employing any ofthe available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding[11].Thus the novel agglomeration technique that transformscrystals themselves directly into a compacted spherical form during crystallization process has beendesired[12].

Methods of Spherical crystallization

The spherical crystallization or particle spherical agglomeration method employs three solvents first is substance dissolution medium, secondis partially dissolution medium for the substance and third one is immiscible with the substance. Spherical crystallization is a solvent exchange crystallization method in which crystal agglomeration is purposely induced through the addition of third solvent known as bridging liquid. Crystal agglomeration, which is usually avoided during normal processing, is performed in a controlled fashion during spherical crystallization to bring about improved flow and compaction properties of the material [13].These properties are highly advantageous for pharmaceutical production. Currently optimization of spherical crystallization is difficult as the mechanism and effect of process parameters are unclear. In process monitoring of the chord length distribution (CLD) to track the rate and degree of change in particle dimension and particle count can provide insight into the dynamics of spherical crystallization. The main requirementin spherical crystallization system is that, it should require a small amount of bridging liquid. The proportion of bridging liquid in the given system can be determined by plotting a ternary or solubility diagram of the bridging liquid in the given system. Following are the methods to prepare the sphericalcrystals.

1. Spherical Agglomeration method(SA)
2. Emulsion Solvent Diffusion method(ESD)
3. Ammonia Diffusion system(ADS)
4. Neutralization Technique(NT)

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5. Traditional Crystallization process(TCP)

1. **Spherical Agglomeration (SA)method:**

bridging liquid [14] Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles [15] Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance. The viscosity of the continuous phase has an effect on the size distribution of the agglomerates. The choice of bridging liquid has an influence on the rate of agglomeration and on the strength ofthe agglomerates.[16]

2. **Emulsion Solvent Diffusion (ESD)method:**

In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent.The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets. The method is considered to be simpler than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase [17][18]

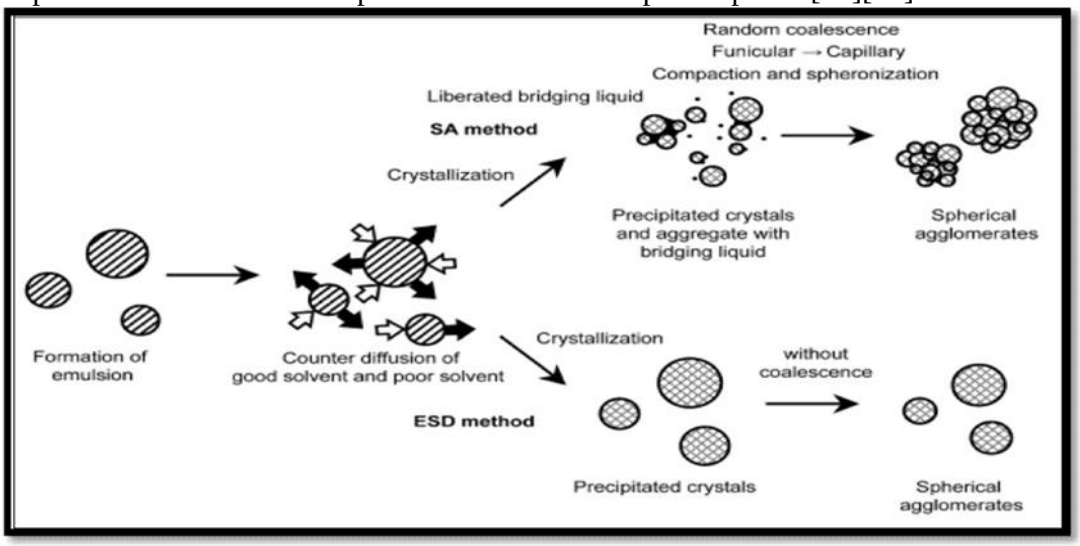

Figure 1 : Mechanism of formation of spherical agglomerates by spherical agglomeration (SA) and Emulsion solvent diffusion (ESD)method.

3. **Ammonia Diffusion method(ADM):**

In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. Water immiscible

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solvent such as hydrocarbons or halogenated hydrocarbons e.g. dichloromethane induced liberation of ammonia water [19].

4. **Neutralization Method(NT):**

This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of antidiabetic drug lansoprazole was reported by this technique. The drug was dissolved in sodium hydroxide solution. Aqueous solution of hydroxyl propyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of lansoprazole and the lansoprazole was crystallized out. The bridging liquid was added drop wise at a rate of 10 ml/min followed by agglomeration of the lansoprazole crystals. The agglomerates of p lansoprazolerepared by neutralization technique were found to have more specific surface area, more wettability and hence better dissolution rate as compared to the agglomerates prepared by emulsionsolventdiffusionmethodandsolventchangemethod.Theagglomeratespreparedbyprepared by neutralization technique were found to have more specific surface area, more wettability and hence better dissolution rate as compared to the agglomerates prepared by emulsionsolventdiffusionmethodandsolventchangemethod.Theagglomeratespreparedbythe neutralization method were instantaneously permeated with water showing strikingly greater wettability. The reason for this superior wettability of agglomerated crystals and tablet is due to fact that, at the time of agglomeration process, hydrophilic hydroxyl propyl methyl cellulose in the crystallization solvent adheres firmly to the agglomerated crystals.[20]

5. **Traditional crystallization process(TCP):**

These methods also can be used to produce spherical crystal agglomerates, which are carried out by controlling the physical and chemical properties and can be called the non-typical spherical crystallization process.[20]

MATERIAL AND METHODS

Lansoprazole (Triveni chemicals), Beta cyclodextrin (Research lab fine chem industries), Mannitol, Talc, Magnesium, stearate and MCC (Rajesh chemicals), Methanol (Priyachemicals), PEG 4000 (Merck ltd.), PEG 6000 (Central drug house pvt ltd) and ColorcoatEC4W (Corel pharma chem.)

Preparation of Spherical crystals:

100 mg Lansoprazole was dissolved in 3 ml methanol (good solvent) and 2ml chloroform (bridging liquid).The resultant solution was poured in to 25ml distilled water (poor solvent) containing 1% /2% /3% w/v at B-CD/ PVP / PEG / EU with strring for 20 min at 25^0 c. The obtained recryastallized crystal were collected by vaccume filtration and dried in an oven 60^0 c for 4 h. The dried crystals were stored at room temp before use.. Above process was repeated more than 3 times to obtain adequate materials for characterization and to observe repeatability. Formulation codes with proportion of excipients used for spherical crystallization of Lansoprazole are as given in table no.6 and respectively.

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Table No.1: Formulation codes with proportion of the excipients used for sphericalcrystallization of Lansoprazole

Sr.no.	Formulation code	Good solvent	Bad solvent	Bridging liquid	Polymer
1	A1	Methanol	Water	-	-
2	A2	Methanol	Water	Chloroform	-
3	A3	Methanol	Water	Chloroform	-
4	AB1	Methanol	Water	Chloroform	β-CD 1%
5	AB2	Methanol	Water	Chloroform	β-CD 2%
6	AB3	Methanol	Water	Chloroform	β-CD 3%
7	AG1	Methanol	Water	Chloroform	PEG 1%
8	AG2	Methanol	Water	Chloroform	PEG 2%
9	AG3	Methanol	Water	Chloroform	PEG 3%
10	AP1	Methanol	Water	Chloroform	PVP 1%
11	AP2	Methanol	Water	Chloroform	PVP 2%
12	AP3	Methanol	Water	Chloroform	PVP 3%
13	AE1	Methanol	Water	Chloroform	EU 1%
14	AE2	Methanol	Water	Chloroform	EU 2%
15	AE3	Methanol	Water	Chloroform	EU 3%

β-CD-β-cyclodextrine,PEG- Poly ethylene glycol, PVP-Poly vinyl pyrrollidone and EU-Eudragite RS100.

1. Determination of solubility in distilled water:

Solubility of pure drug and all batches of spherical crystals in distilled water obtained by adding an excess of the pure drug and dried spherical crystals in 10 ml of distilled water in conical flask. This conical flask kept on orbitary shaker at 25 ± 0.5°C for 24 hrs. to ensuresaturation and sonicated using sonicator for 2 h. After the equilibrium solubility was attained, clear supernant were filtered through 0.45µm filters and appropriate dilutions resultant sample was analysed by UV spectrophotometer at 285 nm [21]

2. Scanning Electron Microscopy (SEM)

Drug and spherical crystals were coated with a thin gold-palladium layer by sputter coater unit (VG- Microtech, United Kingdom), and the surface photography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (SEM; Cambridge, United Kingdom) operated at an acceleration voltage of 10 kV

3. Fourier transforms Infrared spectroscopy (FT-IR):

Fourier transforms Infrared spectroscopy of raw crystals and spherical crystals of Lansoprazole was recorded using Agilent technology carry 630 FT-IR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 4000 to 400 cm-1[22][23]

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4. X-ray powder diffraction(XRPD):

X-ray powder diffraction of raw crystals and spherical crystals of Lansoprazole were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu *K*α – radiations (1.542 A°) and analyzed between 2-60° (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5 x 103 cycles/s and the chart speed was kept at 100 mm/2θ [22][23]

5. Differential Scanning Calorimetry(DSC):

Thermal properties of raw crystals and spherical crystals of Lansoprazole were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (5-10mg) was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 0 to 300°C at a heating rate of 10°C/ min[22][23]

6. In-Vitro dissolution studies sphericalCrystals:

The dissolution studies of spherical crystals of Lansoprazole were performed by using USP type II dissolution test apparatus (United States Pharmacopoeia, 2006) in 900 ml of pH 6.8 phosphate buffer respectively. Temperature was maintained at 37 ±0.5°C and 75 rpm stirring was provided for each dissolution study. Spherical crystals equivalent to 100 mg of Lansoprazole were used for each dissolution study. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41(pore size 0.45µm), concentration of drug was determined spectrophotometrically at 285 nm for Lansoprazole on UV Visible spectrophotometer.

RESULT AND DISSECTION

FTIR spectra of pure Lansoprazole:

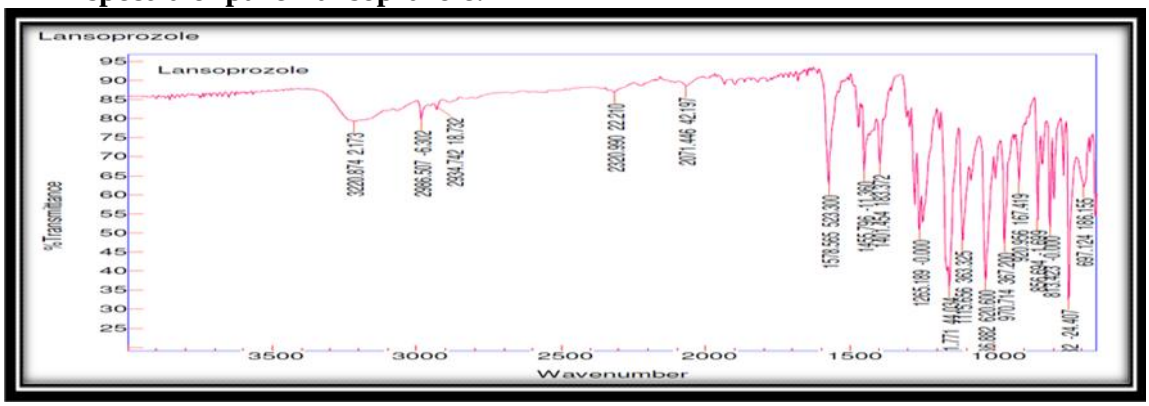

Figure 2:FTIR spectra of pure Lansoprazole

FTIR spectra of AB3 batch (Good solvent-Methanol, Bad solvent-Water, Bridging liquid=Chloroform)

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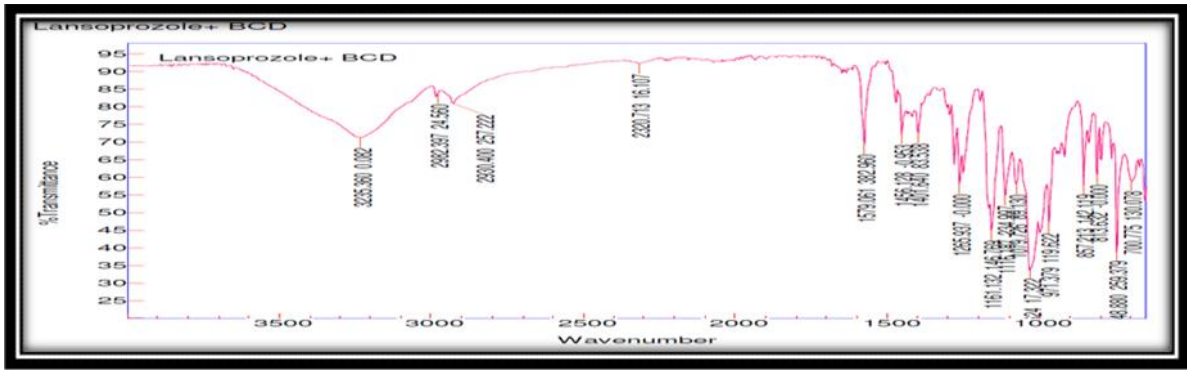

Figure 3: FTIR spectra of spherical crystals of AB3 batch

Table No.2: Major Observation of FTIR groups

Sr. No.	Functional	Peak Position(cm-	Indication
1	Alkanes	700	C-C(Stretching)
2	Aromatic ring	1579	C-C(Stretching)
3	Alkynes	2320	-C=C- (Stretching)
4	Alkanes	2930	C-H (Stretching)
5	Hydrogen bonded alcohols, phenol	3235	O-H(Stretching)

The FTIR spectrum of Lansoprazole has absorption bands at,700,748,813,857, 971,1031,1069,1116, 1161, 1265, 1401, 1456, 1579, 2320, 2982 and 3235 cm-1. Characteristic absorption peaks of Lansoprazole are 3235 for O-H stretching in Hydrogen bonded alcohols, phenol, 2930 for C-H stretching in alkanes group, 2320 for -C=C-Alkynes groups, 1579 for C-C stretching in aromatic rings,700, 748, 813, 857, 971, 1031, 1069, 1116, 1161, 1265, 1401, 1456 for C-C stretching in Alkanes groups. Raw crystals of Lansoprazole and its spherical agglomerates exhibited identical FTIR spectra as shown in figure15-21. It revealed that no any chemical transition has occurred during recrystallization of Lansoprazole. For Lansoprazole agglomerates it has indicated that the altered XRPD spectra and DSC thermogram for these samples were not associated with any changes at the molecular level, confirmed by FTIR study.

1. **X-ray powderdiffraction**

XRPD study is required for determination of crystal lattice and amorphous nature of drug or excipients. By using XRPD we can measure the average spacing between layers or rows of atoms, determine the orientation of a single crystal or grain. The XRPD study of pure Lansopazole shown in Figure 22. It reveals that the intensity of the peaks for the pure drug was sharp (2θ=16.83278 and Intensity=2187) which indicate crystalline nature of pure drug. But

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when Lansoprazole was incorporated into the polymer β-CD, after the preparation of spherical crystals the intensities of the peaks decreases (2θ=21.1504 and Intensity=272) due to the decreased crystallinity of the Lansoprazole in agglomerate form (figure 23). This was becauseof dilution with polymers and dilution carried out by the β-CD though the intensity of peaks in XRPD was reduced, there is no considerable change in d-spacing values suggesting no change in crystal form of drug but crystal habit of drug might be changed thus suggesting absence of polymorphic transition. How theta ever, no obvious peaks representing crystals of Lansoprazole were seen for the solid spherical crystals, indicating the absence of crystalline structure of Lansoprazole in the formulation.

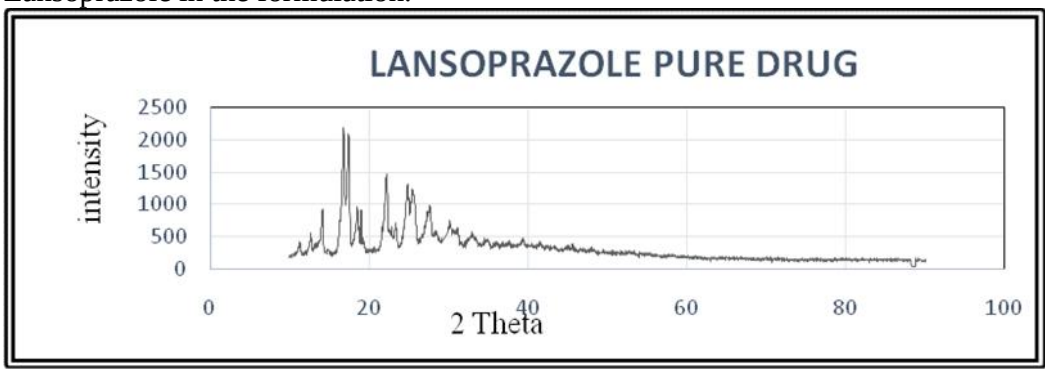

Figure 4: X-ray powder diffraction pattern of pure Lansoprazole.

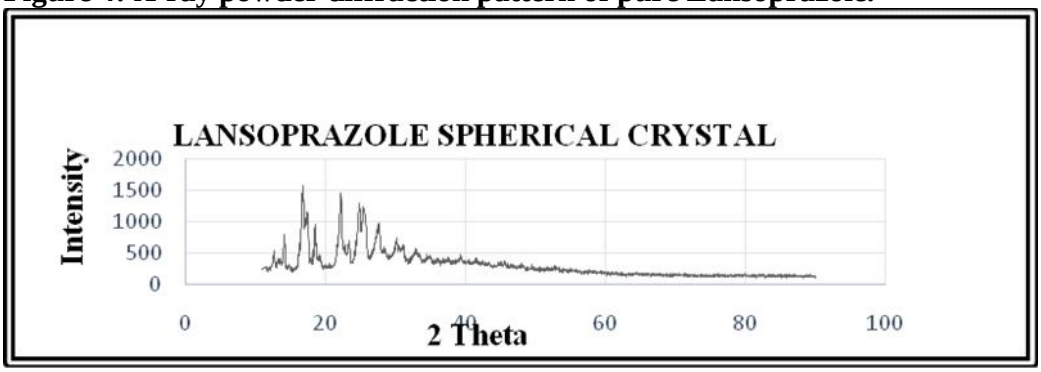

Figure 5: X-ray powder diffraction pattern of optimized batch

2. Differential Scanning Calorimetry(DSC)

The DSCthermogramofsphericalagglomeratesof Lansoprazole are shown in figure 24 and25 respectively. The DSC thermogramof pure Lansoprazole showed sharpmelting endotherm at 184^0C with heat of fusion24.23J/g.This clearly indicates crystalline nature of the pure drug. Inthe thermogram of the β-CD it showed endothermic peak at the 181^0C which corresponds to loss of water and absence of melting endothermic peak indicating hygroscopic nature of β-CD. These findings indicated that raw crystals of Lansoprazole have changed for spherical agglomeratesduring recrystallization Thus DSC results were well supported with XRPDindicating polymorphic transition of Lansoprazole during recrystallization. Thisclearly indicated crystalline nature of the spherical agglomerates. This observation also confirmed the absence of any chemical interaction of drug with additives during agglomeration process, further supporting the results of IR spectroscopy.

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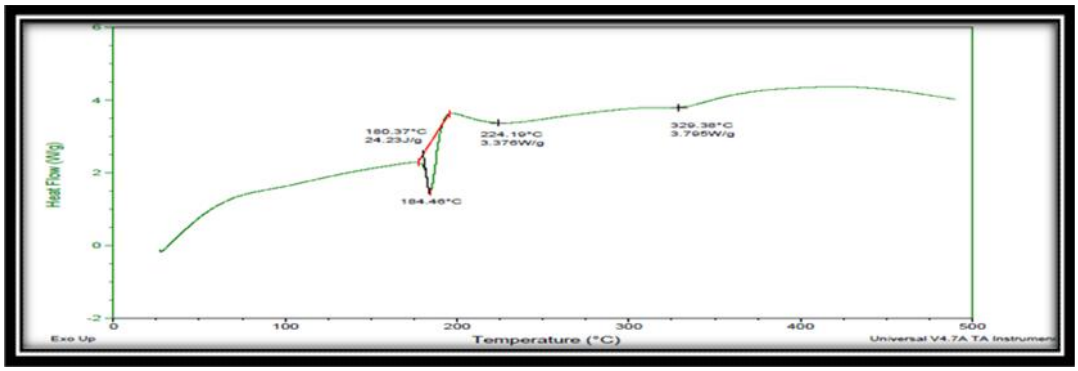

Figure 6: DSC Thermogram of Lansoprazole.

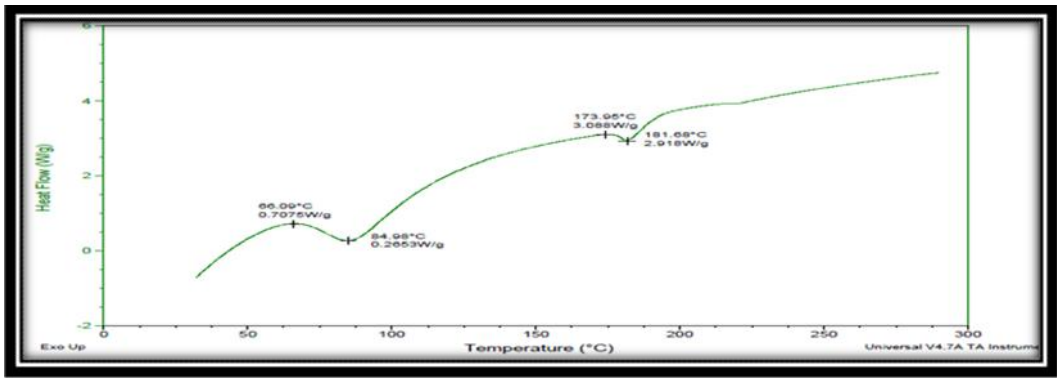

Figure 7: DSC Thermogram of optimized batch AB3

3. Scanning Electron MicroscopyAnalysis:

Scanning electron microscopy (SEM) is an electron optical imaging technique that provides photographic images and elemental information. The signals that derive from electron sample interactions reveal information about the sample including external morphology (texture) and crystalline structure and orientation of materials making up the sample. Used to determine particle size distribution, surface topography, texture and examine the morphology of fractured or sectioned surface. SEM analyses were observed that the spherical crystal**.** An examination of the SEMs, confirm that the starting material of Lansoprazole powder appeared as smooth-surfaced, small spherical crystals markedly smaller in particle size (Fig. A) than any of the treated crystals (Fig. B). whereas spherical crystals of Lansoprazole were produced with β-CD 3% (Fig. B). These figures clearly indicate that the use of polymer in the crystallization mediahad major effect on the overall shape of Lansoprazole crystals in comparison with pure drug. However, the converted solid raw crystals into larger particle size and smooth- surfaced particles with spherical crystalline shape (fig. B), indicating complete adsorption of polymer containing amorphous drug. This could be one of the reasons for the excellent flowability and packabilityofthe agglomerates. On the basis of these findings, it could be concluded that good flowability and packability for agglomerates were attributable to the spherical shape and smooth surface, since the area of contacts in the powder bed for spherical crystals was smaller than the needle shaped crystal of Lansoprazole.[24]

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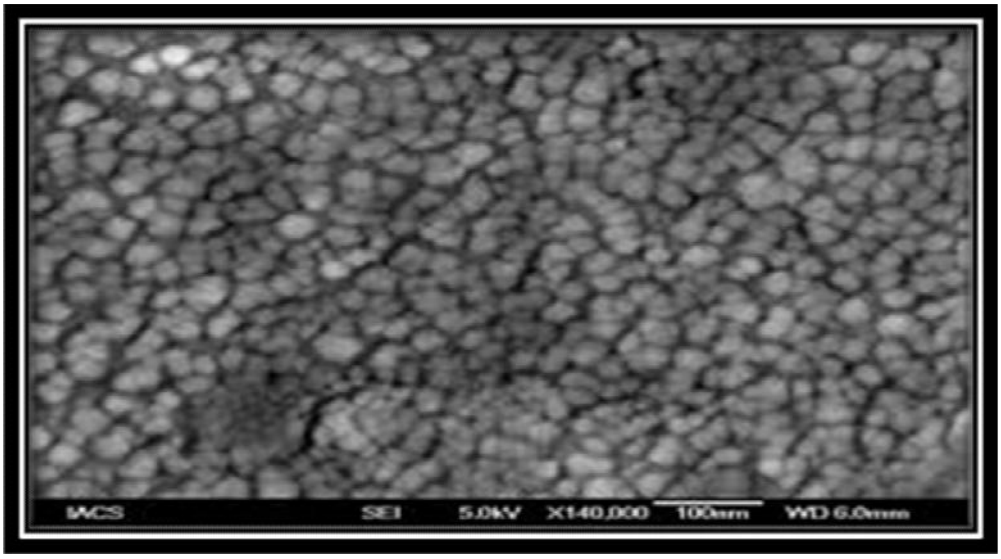

Figure 8: Scanning Electron Microscopy of Lansoprazole pure drug.

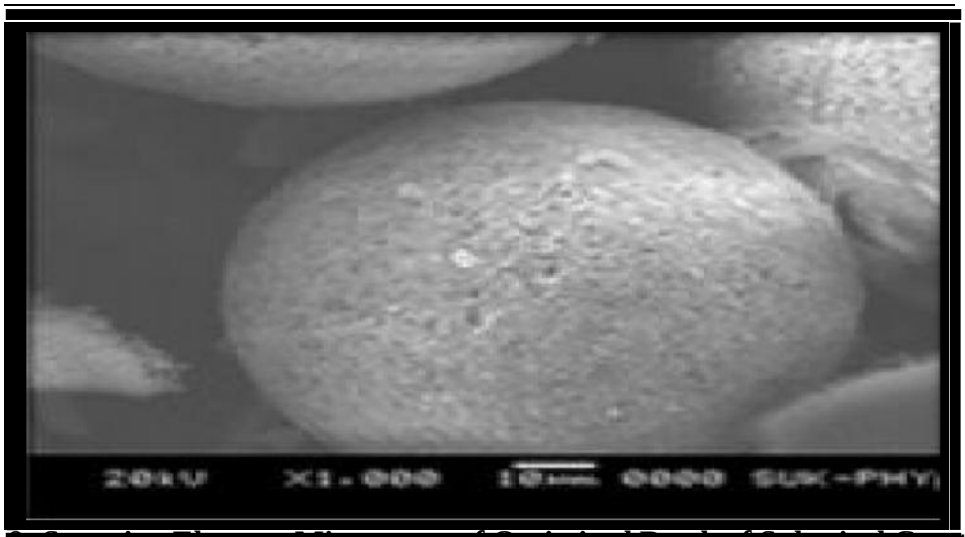

Figure 9: Scanning Electron Microscopy of Optimized Batch of Spherical Crystals

4. In-Vitro Release Studies of Prepared SphericalCrystals:

The dissolution studies of raw crystals and spherical agglomerates of Lansoprazole were performed by using USP type II dissolution test apparatus (United States Pharmacopoeia, 2006) in 900 ml of pH 6.8 phosphate buffer respectively.

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Table No.3:DissolutionTestof Prepared Spherical Crystals

Details of Dissolution Test	
Apparatus	USP Paddle 2 Apparatus
Speed	75 rpm
Volume of medium	900 ml
Aliquot taken at each time interval	1 ml
Medium used	Phosphate buffer pH 6.8
Temperature	37 ± 0.5 °C
Drug use	10mg
Time (Min)	10,20,30,40,50 and 60

Table No.4:%Drug release of spherical crystals (A1-AB3 batch):

SR. NO.	**Batch**	**Time**					
1	**0**	**10**	**20**	**30**	**40**	**50**	**60**
2	**A1**	**20.48**±2.57	**30.87**±3.44	**47.32**±2.55	**47.68**±3.58	**59.94**±3.71	**67.11**±2.69
3	**A2**	**20.64**±2.65	**31.05**±3.65	**45.97**±3.46	**63.15**±3.69	**77.38**±3.52	**86.02**±2.88
4	**A3**	**20.71**±2.65	**31.50**±3.48	**46.75**±3.48	**63.25**±3.48	**83.00**±3.22	**90.62**±2.84
5	**AB1**	**24.58**±3.14	**36.55**±2.48	**46.91**±2.49	**55.10**±2.66	**59.61**±2.46	**73.72**±3.65
6	**AB2**	**23.87**±2.94	**36.44**±2.98	**43.87**±3.12	**53.17**±2.77	**56.58**±2.98	**70.94**±3.78
7	**AB3**	**23.44**±3.54	**35.10**±2.45	**37.72**±3.31	**52.37**±3.41	**60.98**±3.76	**76.88**±2.72

** Each value is average of three separate determinations ±SD*

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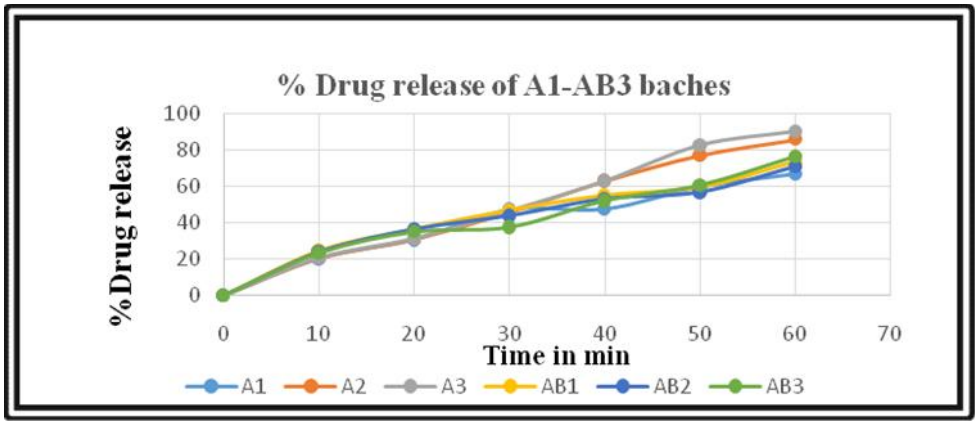

Figure 10: Drug Release Profile of spherical crystals (Batches A1-AB3)

CONCLUSION

Agglomerates β-CD were found to be better comparative to all agglomerates in all aspects.stable spherical aggolerates of lansoprazole were successfully prepared by emulsion solvent diffusion method with β-CD /PVP/ PEG/EU(1% 2% & 3%).Solubility, dissolution rate and bioavalibility of all agglomerates comparatively improved than raw crystals of drugs.conclude the spherical crystallization of lansoprazole with selective additives is a satisfactory method of improve flowability,compatability and packability for direct tableting along with enhance solubility ,dissolution and bioavalibility.

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