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Modification of drug particle morphology by spherical crystallization technique to obtain directly compressible material

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ABSTRACT

Spherical crystallization is a novel particle engineering/design technique developed by Kawashima et al, to overcome the problems associated with direct compression. Basically, it's single step process used for size enlargement of single, two or more, small dose or large dose drugs, in combination with or without diluent. The process of spherical crystallization involves simultaneous crystallization and agglomeration of drug/s with/without excipients/s from good solvent and/or bridging liquid by addition of a non-solvent. The spherical agglomerates obtained by spherical crystallization can be directly compressible tablet intermediates having satisfactory micromeritic (flowability), mechanical (friability, crushing), compressional (compressibility, compactibility), and drug release properties. Enhanced drug release from agglomerates and compacts thereof can be achieved using suitable polymer composition in the process design. Thus, it can be concluded that, spherical crystallization is a simple and cost effective process, which can be modify the morphology for particle design of all majority of drugs and combinations.

Key words: Direct compression, spherical crystallization, spherical agglomeration, bridging liquid, particle design.

INTRODUCTION

Tablets are the solid unit dosage forms of choice with good dose precision & least content variability, low cost, ease of administration & tamper proof packaging. Over the last several decades tablets have undergone rapid developmental changes & direct compression is one of the most revolutionary technologies. Direct compression is the modern most efficient process of tablet manufacturing & offer advantages like it is economical, facilitates processing without the need of moisture & heat, less number of processing steps & able to form stable compacts at low punch forces. Spherical crystallization is one of technique of particle design & a non convective method imparts the properties like good flowability, mechanical strength, compressibility & enhance the particle size & eliminates many processing steps like granulation & drying etc moreover for moisture sensitive drugs wet granulation cannot be applied. Spherical crystallization can be employed for some of the drugs such as NSAIDS which exhibit the poor compressibility, flowability, solubility & for drugs are not suitable for direct compression. Recently in pharmaceutical companies for reducing the production cost & improving the production process by modified crystalline technique were used spherical crystallization is one among those techniques which has emerged as one of the areas of active research ,currently of interest in pharmaceutical manufacturing & recently came into forefront of interest & gained attention & importance due to the fact of crystal habit(form, surface, size & particle size distribution can be modified during the crystallization process. When large amount of non water soluble drugs with

poor rheological properties are needed to be formulated the quality & efficiency of solid dosage form is influenced by primary micromeritic properties (size & shape of crystals) & micromeritic properties(bulk density, flowability) of active medical substances & inactive substances.

Spherical crystallization enables co-precipitation of drug & encapsulating polymer in the form of spherical particles [1]. Spherical agglomeration technique is beneficial to ease of formulating microspheres, microsponges, nanospheres, microbaloons and nanoparticles which acts as novel particulate drug delivery systems **[**2]**.** To improve bioavailability as crystalline form is converted into different polymorphic forms, enables the improvement of flowability and compressibility of crystalline drugs, it has been successfully employed to enable processes such as separation, filtration, drying etc to be carried out more efficiently**[**3**]**, drastically improves wettability, dissolution rate & can be easily compounded with other pharmaceutical powders**[**4,5**]**.

Solvents and solvent secletion:
First is substance dissolution medium - good solvent.
Second is partially dissolution medium for substances - Bridging liquid.
Third one is immiscible with substance - poor solvent **[**6**]**.

Table 1: It shows Drug solubility and selection of solvents, bridging liquid and methods:

Drug Solubility	Continuous Phase	Bridging liquid	Method applied
In water	Water immiscible organic solvent	Calcium chloride solution (20%)	Spherical agglomeration technique
In organic solvent	Water	Water immiscible organic solvent	Spherical agglomeration technique
Water miscible organic solvent	Saturated aqueous organic solution	Organic solvent mixture	Quasi-emulsion solvent diffusion method
Water or any other organic solvent	Water immiscible organic solvent	Calcium chloride solution(20%)+binding solution	Spherical agglomeration technique

Methods of spherical crystallization:
Solvent change method (SC):
Solvent change method involves simultaneous crystallization and agglomeration of two or more drugs from a good solvent and bridging liquid by addition of a non-solvent. To obtain fine crystals the solution of the drug and a good solvent is poured into a poor solvent under controlled condition of temperature and speed. The bridging liquid is used for agglomeration of the crystals. The poor solvent has miscibility with good solvent but has low solubility in solvent mixture, so that, during agitation of the solvent system the crystals are formed. The drawback of this system is that it provides low yield, due to co-solvency effect of crystallization solvent. The bridging liquid, the stirring speed and the concentration of solids are the influencing factors for the spherical crystallization [7].

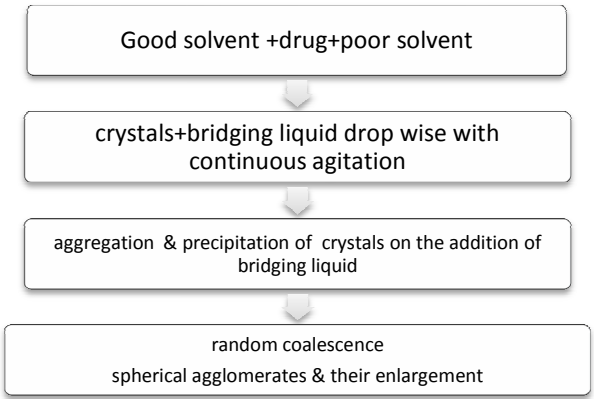
Lesser amount of bridging liquid will yield fine particles where as larger amount of bridging liquid will produce coarse particles. By increasing stirring rate the agglomeration get reduced, because of increasing disruptive forces [8].

Porosity decreases when the concentration of solid increases. The viscosity of the continuous phase has an effect on the size distribution of the agglomerates**[**9**]**. The choice of bridging liquid has an influence on the rate of agglomera tion and also on the strength of the agglomerates.

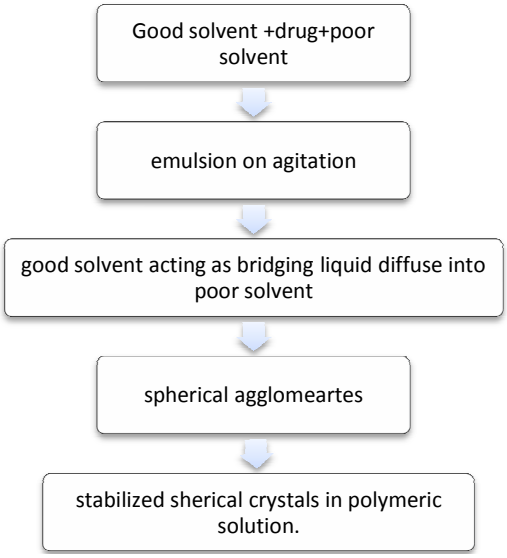
Quasi emulsion solvent diffusion method:
In the case of quasi emulsion solvent diffusion method, affinity between the drug and a good solvent is stronger than that of the drug and poor solvent [10]. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. Due to the interfacial tension between the two solvents, the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase.

The crystallization of drug occurs by counter diffusion of good solvent and poor solvent. In this process, the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization. In the droplets, the process of solidification proceeds inwards and the liquid are not maintained on the surface and the agglomerate formed without coalescence.

Steps involved in Solvent change method:



Steps involved in Quasi emulsion solvent diffusion method:



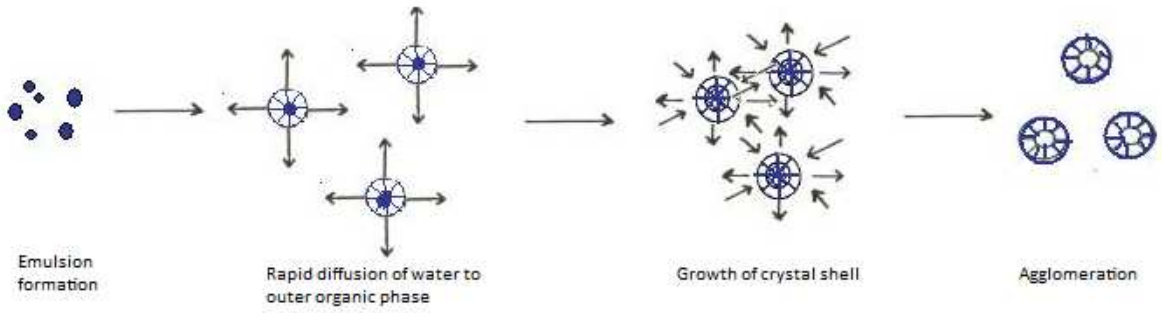


Fig. 1: It shows Mechanism of Quasi emulsion solvent diffusion method.

Ammonia diffusion method (AD):

In this method, the mixture of acetone, ammonia water and dichloromethane shall be used as a crystallization system. In this system ammonia water acts as bridging liquid as well as good solvent. The other components of the system, like poor solvent and a hydrocarbon derivative are selected depending upon the drug's

solubility in that solvent. Acetone (hydrocarbon derivative) is miscible with the system but it reduces the miscibility of ammonia water with poor solvent. The ammonia water exists as immiscible phase forming droplets. The counter diffusion process across the droplet involves movement of poor solvent into and ammonia out of the droplet. Inside the droplet agglomeration takes place as the drug precipitates slowly in ammonia water and causes growth of crystal [11]. The technique is mainly applicable for amphoteric drugs, which have the same properties as enoxacin.

Steps involved in Ammonia diffusion method:

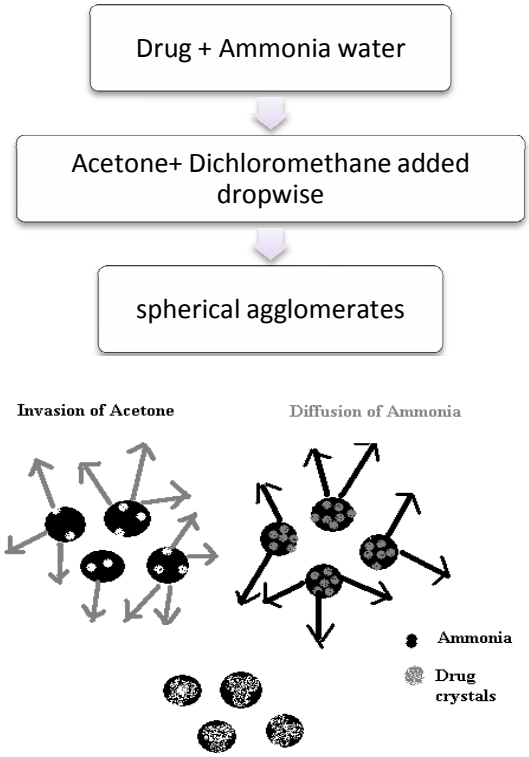


Fig. 2: It shows Mechanism of Ammonia diffusion method

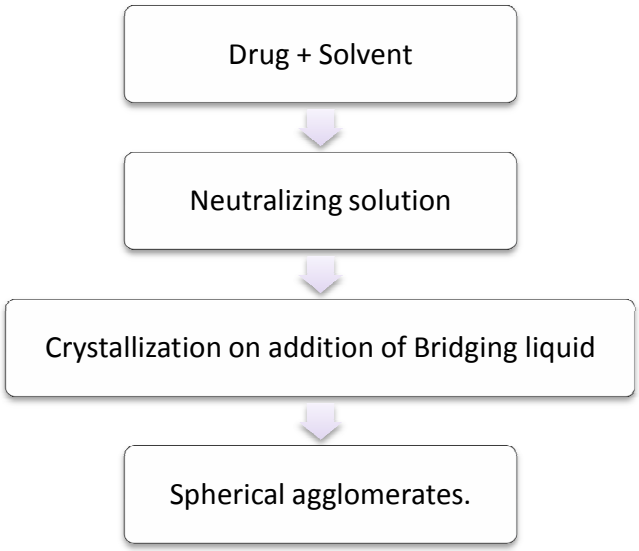
Neutralization method:
The method consists of dissolving the drug in the good solvent and placing in the cylindrical vessel with constant stirring. During stirring an aqueous polymer solution and one neutral solution was added to neutralize the good solvent, which crystallizes out the drug. The bridging liquid shall be added drop wise at a definite rate. The agglomeration of the crystal form of the drug takes place [12].

Traditional crystallization process:
Spherical agglomerates shall be produced in these methods by controlling the physical and chemical properties and can be called as the non typical spherical crystallization processes

Crystal-co-agglomeration technique (CCA):
Applications of spherical crystallization to obtain directly compressible agglomerates without diluents are restricted to water insoluble large-dose drugs only. Most of the excipients, such as diluents and disintegrating agents, are hydrophilic in nature. Hence incorporation of these excipients in the agglomerates formed by using organic bridging liquid is difficult. Due to this limitation, spherical crystallization could not be applied to obtain agglomerates of low-dose or poorly compressible materials [13]. To overcome these limitations of spherical crystallization Kadam et al. developed the Crystallo-co-agglomeration (CCA) technique. It is a modification of the spherical crystallization technique in which a drug is crystallized and agglomerated with excipients or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid.

The process enables design of agglomerates containing two drugs (Mahadik et al., 2004) or a low-dose [14] or poorly compressible drug in combination with diluents[15,16]. The difference in the physicochemical properties of the drug molecules and the excipients become the major challenge in the selection of a solvent system for the crystal-co-agglomeration technique.

Steps involved in Neutralization method:



Steps involved in Crystal-co-agglomeration technique:

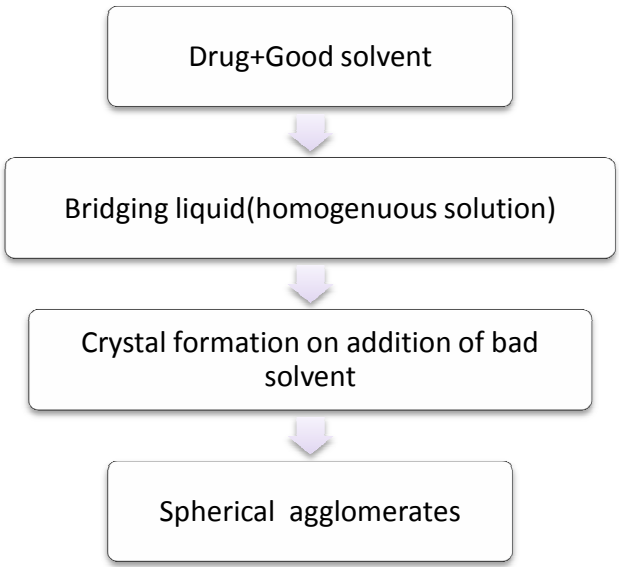


Table 2: It shows the methods & examples of drugs improving its physicochemical properties by spherical crystallization techniques.

Method	Drug	Solvent	Research findings
SA	Aminophylline Kawashima, y.,et al.	Chloroform ,Ethanol, Water	Resultant Aminophylline agglomerates were free flowing & directly compressible due to their spherical shape.
SA	Naproxen Gorodon, M.S.,et al.	Acetone ,Water, Hexane, Octanol, Toulene	Improved flow characteristics & compressibility
SA	Aspirin Deshpande,m.c.,et al.	Acid buffer, Methanol, Chloroform	Improved flow characteristics, compressibility & stability.
AD	Ampicillin trihydrate Ghol.m.,et al.M	Ammonia water, Acetone, Dichloromethane	Improved micromeritic properties, compressibility & compaction properties. Drug release same as marketed product.
SA	Ibuprofen Jbilou, M.,et al.	Water, Ethanol.	Increased compressibility & dissolution rate.
SA/QESDS	Ascorbic acid Kawashima Y.,et al.	Purified water, Ethyl acetate, Methanol.	Improved micromeritic & compaction properties of the original Ascorbic acid crystals.
AD	Enoxacin Ueda Masumi.,et al.	Ammonia water, Acetone, Dichloromethane.	Improved flow characteristics, packability without delay in dissolution rate.
SA/QESDS	Bucillamine Morshima, k., et al.	Ethanol, Dichloromethane, water.	Agglomerates show excellent compatibility, packability.
QESDS	Ibuprofen Kawashima Y,et al.	Ethanol, water with sucrose fatty acid ester.	Improved flow characteristics, packability, compressibility of the resultant microspheres.

SA = Spherical Agglomeration technique, AD = Ammonia Diffusion method, QESD = Quasi Emulsion Solvent Diffusion method

Physico Chemical characterization of Agglomerates:

Thin layer chromatography:

TLC study was carried out in mentioned mobile phase and the Rf value was determined and compared the Rf value of drug with the spherical crystals. This study was carried out to check the interaction between the drug and the polymer and also to confirm the stability of drug in solvents.

Fourier Transform Infrared spectrometer:

It was done for identification of the drug present and also to identify whether the drug has undergone polymorphism. It is much more useful for distinguishing between solvates and anhydrous form then for identifying polymorphs because of the addition of new stretching frequencies resulting from the solvation.

Differential scanning calorimeter:

DSC measures the heat loss or gain resulting due to physical or chemical changes within a sample could be obtained from thermograms using instrumental software. If a mixture of drugs and polymer is agglomerated together then change in properties of agglomerates can be studied with DSC. It is also useful to determine thermal degradation, purity, polymorphism, solvation, Dehydration, Dissociation, Decomposition, and Phase transfer, Glass transition, Heat capacity and drug-excipients compatibility. Crystal of samples ae heated (25-200°C) at the rate of 10°C/min in crimped hemetically sealed aluminum pans under nitrogen atmosphere. Calorimeter was calibrated using Indium & lead standards.

Particle shape & surface topography:

Geometrical properties of agglomerates

Geometrical properties of spherical crystals can be determined by image processing system. Around 300 particle of different range size fraction were run over with an optical pen. The system determines the smallest (D_{min}) and the largest (D_{max}) diameter of each individual particle. A Parameter R was developed, which indicates the roundness of the particles sovereignty of the size of the particle. A value of R near 1 is indicative of perfectly spherical agglomerate.

Electron Scanning Microscopy

The surface topography, type of crystals (polymorphism and crystal habit) of the spherical agglomerates & the conventional crystals is analyzed by using scanning electron microscopy. Using an image analyzer micrographs of more than 100 particles were transformed into the software and the shape factor is specified as 4π (area/perimeter).

X-ray Powder Diffraction

This is an important technique for establishing batch-to-batch reproducibility of a crystalline form. The form of crystal in agglomerates determine by using technique. An amorphous form does not produce a pattern. The X-ray scattered in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each

diffraction pattern is characteristics of a specific crystalline lattice for a compound. X-ray diffractometer is operated at 40kV, 30mA, and a scanning speed of 0.06°/min over the range of 5-40 2θ using Cu kα1 radiation of wavelength of 1.540 A°.

Parameters determining the agglomerates behavior:
Particle size, Particle shape & Size distribution:
Change of crystal habit of pharmaceuticals gives different physico-chemical properties. Size & crystal habit of pharmaceuticals changes on recrystallization in spherical crystallization.
1. In advance technology, Size & volume of particles can be determined by image analyzer
2. .Size of particles & their distributions can be determined by simple sieve analysis.
3. Particle size analysis can be determined by Ro-Tap sieve shaker.

Density:
Density of spherical crystals is mass per unit volume. Different type of densities such as true density, granular density, apparent bulk density, tapped density can be evaluated.

True density = M / Vt.

Granular density = M / Vg.

Bulk density = M / V b.

Tap density = weight of sample in gm/tapped volume of sample in ml.

When compared to original drug crystals the size of agglomerates is more. Therefore, with increase of agglomerates, density of drug substances decreases.

Amorphous form:
It is developed by addition of polymers during recrystallization which have enhanced solubility compared to crystalline form.

Flowability:
a. Angle of repose: It is determined by following equation

$\tan \theta = h/0.5\ d$

Where h-height of pile
d-diameter of pile
Value
$\leq 30 \rightarrow$free flowing materials
$\geq 40 \rightarrow$poor flowing materials

Compressibility or Carr's index: A simple indication of ease with which a material can be induced to flow is given by application of compressibility index

$I = (1-V/V_o)* 100$

Where V = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping.

The value below 15% indicates good flow characteristics and value above 25% indicate poor flowability.

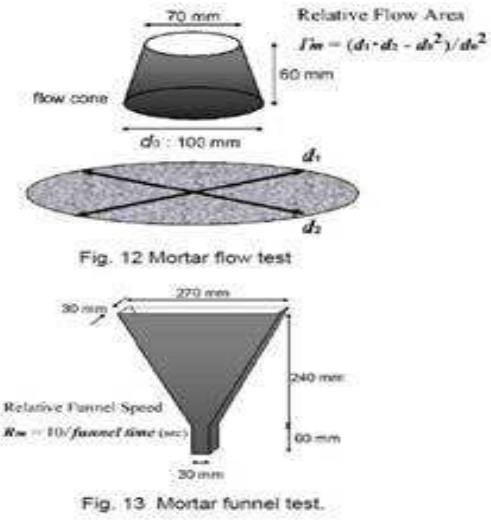


Fig. 3: It shows Determination of Angle of repose

Hausners ratio: Calculated from bulk & tapped densities.

HR = Tapped density/Bulk density

Value < 1.25-good flow (20% Carr's index).
> 1.25-poor flow (33% Carr's index).

Between 1.25-1.5 –to improve the flow glidant must be added.

Porosity:
Porosity affects the compressibility in granules. Porosity is of two types intragranular & intergranular. These are measured with the help of true & granular densities.

Intergrannular Porosity = 1 - granular density/ true density

Intergrannular Porosity= 1 - bulk density/ granular density

Total Porosity= 1 - bulk density/ tapped density

Packability:
Shear cohesive stress, shear indexes & angle of friction are lower than that of single crystals which can be improve packability of agglomerates. Simple packability was assessed by tapping process with kawakita & kuno methods & using parameters a, b & k in equations.

N/C=1/(ab) + N/a

C=(V_o-Vn)/ Vo, a=(V_o-V∞)/ Vo.

ρ f - ρ n = (ρ f - ρ o). exp. (-kn)

N =Number of tapping.
C =Difference in volume (degree of volume reduction.)
a and b = constant for packability and Flowability
Vo = Initial volume.
Vn = Final volume after n the tapping.
V∞ = Powder bed volume at equilibrium.

ρ f, ρ n, ρ o = Apparent densities at equilibrium, nth tapped and initial state respectively[17].

Wettability:
Density was determined by using relative density bottle. Surface tension was determined by employing stalagmometer. Wettability can be determined by following formula.

$B=\rho g/2\gamma$

γ = surface tension of saturated solution of formulation in water; dyne/cm;
ρ = density of saturated solution of formulation in water, gm/cm 3,
ε = porosity of tablet, h = height of liquid drop in cm [4, 5].

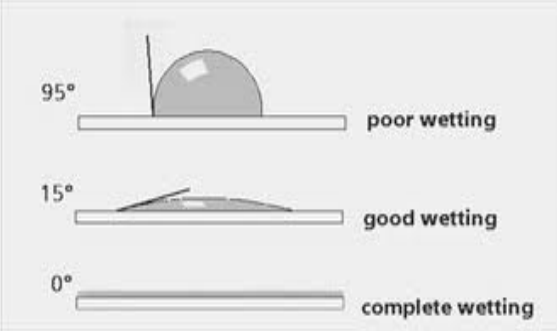


Fig. 4: It shows Wettability & contact angles

Moisture uptake study:
The moisture uptake is determined by taking the weighed quantity of drug & spherical crystals & placing them in crucible at accelerated conditions of temperature & humidity i.e., 40±10° C & 75±3% respectively. The weight gain of drug & spherical crystals is measured [18].

Mechanical strength [19]**:**
a. Tensile strength: Tensile strength of spherical crystals is measured by applying maximum load required to crush the spherical crystal. This method is a direct method to measure the tensile strength of spherical crystals.

b. Crushing Strength: It is measured by using 50ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel is then used as hallow support and the guide tube with close fitting tolerances to the Plunger. The hallow plunger with open end served as load cell in which mercury could be added. A window cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (gm). At the rate of 10 gm/sec, mercury is introduced from reservoir into the upper chamber until the single granule crushed; loading time should be <3 minutes. The total weight of the plunger and the mercury required to fracture a granule is the crushing load [20].

Compression behavior analysis:
Good compactibility and compressibility are the fundamental properties of directly compressible crystals. The compaction behavior of agglomerated crystals and single crystals is obtained by plotting a graph by taking the relative volume against the compression pressure. Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals. The surface are freshly prepared by fracture during compression of agglomerates, which intensifies the plastic inter particle bonding, resulting in a lower compression force obligatory for compressing the agglomerates under plastic deformation compared to that of single crystals. Compaction behavior of agglomerated crystals were evaluated by using following parameters

a. Heckel Analysis: The following Heckel's equation used to analyze the compression process of agglomerated crystals and estimated their compactibility[21].

In [1/(1-D)]=KP+A

Where:
D is the relative density of the tablets under compression Pressure
K is the slope of the straight portion of the Heckel Plot

The reciprocal of K is the mean yield is the mean yield pressure (Py).

The following equation gives the intercept obtained by extrapolating the straight portion of the plots [22].

A=1n [1/ (1-D0)]+B

Where: D0 is the relative density of the powder bed when P=0.

The following equation gives the relative densities corresponding to A and B.

DA=1-e-A

DB=DA-D0

b. Stress Relaxation Test: Impose specific quantity of spherical agglomerated crystals sample in a die of specific diameter, magnesium stearate was coated on the surface of die in advance, then used the universal tensile compression tester to compress the samples at a constant speed. After the certain limit of pressure attained, the upper punch held in the same position for 20 min, during which measured time for the reduction amount of the stress applied on the upper punch. The result corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions [13].

The relationship between relaxation ratio Y (t) and time t, calculated the parameters As and Bs, and assessed relaxation behavior is

t / Y (t) =1/AsBs-t/As

Y (t) = (P0-Pt)/P0

P0 is the maximum compression pressure, and Pt is the pressure at time t [14].

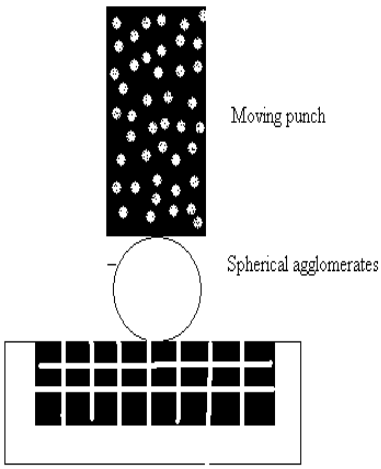


Fig. 5: It shows Compression of the spherical agglomerates

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