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SPHERICAL AGGLOMERATION TECHNIQUE: A INNOVATIVE ENGINEERING PERSPECTIVE FOR IMPROVEMENT OF MICROMERITIC PROPERTIES OF DRUGS

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ABSTRACT

Direct compression of powder is very simplest and easiest way of manufacturing tablets. Good flow ability and compressibility plays a major role for direct compression of drugs there are several techniques available to impart desired compressibility to drugs. Spherical agglomeration technique are reliable technique in which the drug crystals are modified using different solvents to directly compressible spherical agglomerates, which less economical and time saving. The article gives a detailed review and focused on desired outcomes, trouble shooting/ possible formulation challenges and limitation of techniques, process variable, method of preparation along with the evaluation and characterization of agglomerates, and also focused on solvent used by researchers for preparation of spherical agglomerates of different drugs and improved micrometric properties.

KEYWORDS: Compressibility, flow property, direct compression, spherical agglomeration, formulation challenges.

INTRODUCTION

Micromeritics involve the study of the science and technology of small particles. Bulk flow, formulation homogeneity and surface area-controlled processes such as dissolution and chemical reactivity are directly affected by micromeritic properties of solids such as size, shape and surface morphology. In general, each new drug candidate should be tested during preformulation with the smallest particle size as the particle size is useful to facilitate the preparation of homogeneous samples and maximize the drug's surface area for interaction.[14] The micromeritic properties also have a significant impact on the process ability and product

quality of pharmaceutical dosage forms. Particle size and surface area influence the release of drug from a dosage form that is administered orally, rectally, parenterally and topically, higher surface area brings about intimate contact of the drug with the dissolution fluids *in-vivo* and increases the drug solubility and dissolution. it also influence the drug absorption and subsequently the therapeutic action.

Spherical agglomeration(SA) is a novel engineering approach for improvement of drugs micromeritic properties. It is a single step process used for increase bulk of single, two or more, small dose drugs, in combination with or without diluent.[6] The process of SA involves simultaneous crystallization and agglomeration of drug with or without excipients from good solvent and bridging liquid by addition of a non-solvent. Drug dissolving solvents are called good solvent, drug not dissolving solvents are bad solvent and the bridging liquid is form the liquid bridges between crystallized particles and insoluble solid during the process of agglomeration. The solvent system selection for the SA process depends on solubility and stability of drug.[2]

Desired Outcomes Of Drug Agglomerates Obtained By Spherical Agglomeration Technique[12,13]

1. Excellent flow characteristics.
2. Improved Compressibility.
3. Uniformity in Drug content due to continuous stirring.
4. Improved absorption and bioavailability of drugs due to minuscular form of drug.
5. Reduction in localized toxicity of drug.
6. Uniform size distribution due to large surface area.
7. Improvement in the therapeutic efficacy of drug.
8. Mechanical resistance to physiological variables such as gastric emptying time.
9. Less chances of dose dumping.

Steps involved in preparation spherical agglomeration

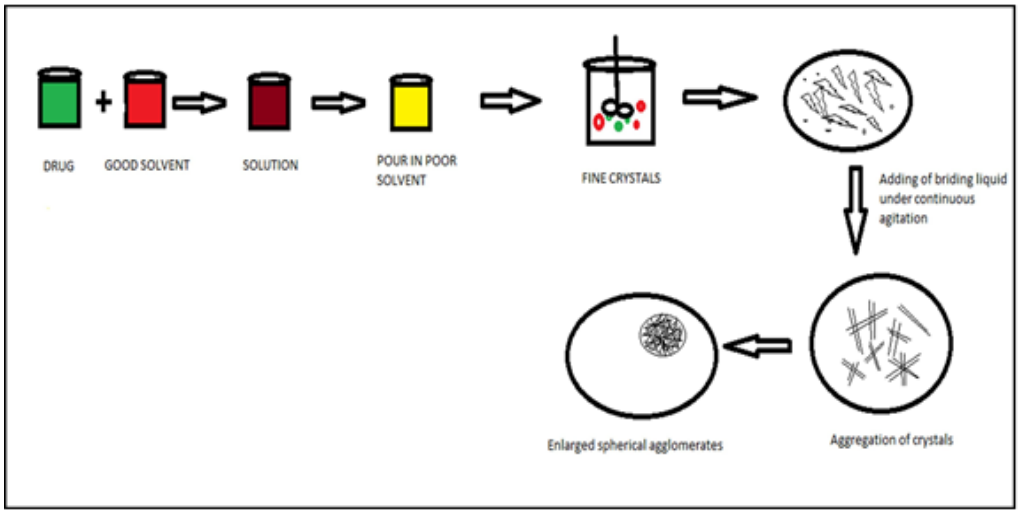

Figure 1: Generalized Diagram for SA process.

Table 2: Trouble Shooting/Possible Formulation Challenges/ Limitations.

Possible Formulation Challenges/ Limitations	Remedy
○ Use of Organic Solvent	○ Proper drying and evaporation of organic solvent ○ Quality control check Residual solvent analysis by GC
○ Drug loss	○ Use of minimum possible volume of external phase. ○ Quality control check Content uniformity assay
○ Addition of disintegrants and super-disintegrants	○ Addition should be carried out of in organic phase
○ Difficulty of Simultaneous crystallization and co-agglomeration using same solvent, at same pH or temperature conditions Incorporation of disintegrant to the agglomates ○ Scaling of Filtration and drying stages are difficult ○ Reproducibility due to process variables	○ Identification of critical attributes and critical process parameters and Optimization of process variables for predetermined Target profiles.

PROCESS VARIABLES

1) Mixing Speed

Mixing of the system is needed to support the process of emulsification or dispersion of the internal phase in the external phase. It has been reported that, the speed of Mixing affects size, sphericity, and strength of agglomerates. A high speed of mixing increases sphericity, but reduces strength of agglomerates. It has been observed that time required for the completion of the agglomeration process gets reduced with higher speed of mixing.

2) Mixing time

The completion of the agglomeration process depends on the time for which the system was kept agitated. Inadequate agitation or mixing does not ensure uniform mixing of ingredients and may cause incomplete growth of agglomerates. Even, this has resulted into incomplete evaporation of an organic solvent from the vessel. If duration of mixing exceeds the endpoint of the agglomeration process, then it promotes fine formation and initiates the de-agglomeration process. Hence, judging the end point of the agglomeration process becomes critical in SA. It can be decide by clarity of supernatant, residual organic solvent.[8,9,10]

Table 3: Overview of mixing speed and mixing time of reported studies.

Drug	Mixing speed (RPM)	Mixing time (Min)	Reference
Bromohexine HCL	900	90	44
Mebendazole	450	15	33
Felodipine	200	25	35

3) Diluent selection

The utilization of diluent has been proposed in SA for size enlargement of low measurements drugs. Diluent choosen must be physico-chemically and physiologically inert and cheap. Also, it should to be insoluble in the watery stage to keep away from the misfortunes through the constant or external phase. The required quality of powder has been utilized for the improvement of the SA procedure. Considering desired quality attribute talc has been used as a diluent in the development of the SA process. Talc as an excipient or diluent in bead or pellet making gets strengthened further. Now, starch and sodium starch glycolate has been used in preparation of rapidly disintegrating agglomerates of naproxen by the SA process.[8,9,10]

4) Solvent system

Solubility and stability of drug in solvent is important criteria for selection of solvent system. Since, majority of drugs are soluble in organic solvents and poorly soluble in water. Use of organic solvent (relatively non toxic) has been recommended as a good solvent and or bridging liquid and water as an external/processing phase (non solvent). The bridging liquid should carry out preferential wetting of crystals solids and form liquid bridges during the process of agglomeration, and simultaneously, it should be immiscible with a non-solvent. If bridging liquid is used as a good solvent, it means, it performs dual role of a good solvent and bridging liquid. The good solvent used should be volatile and immiscible with non-solvent to

avoid drug loss due to co-solvency. Amount of bridging liquid required can be decided by the trial and error method or the ternary phase diagram. It has been observed that if addition of bridging liquid becomes insufficient, then it leads to generation of smaller size agglomerates with more percentage of small particles. And excess addition of bridging liquid generates bigger size agglomerates and requires more processing time for completion of the agglomeration process.[8,9,10]

5) Polymers

Some of the drugs have poor compressibility and physichomechanical characteristics. These proparties play very important role in the direct compression of tablets. So different polymers like hydroxy propyl methylcellulose (HPMC), poly ethylene glycol (PEG), ethyl cellulose (EC) and poly vinyl pyruvate (PVP), Sodium starch glycolate (SSG) can be used in preparation of drug agglomerates. This enhances the micromeritics mechanical and drug discharge properties of the agglomerates.[8,9,10]

Table 4: Overview of polymers used in reported studies.

Drug	Polymers	Reference
Aceclofenac paracetamol	PEG 6000,HPMC,SSG	[11]
Ibuprofen-paracetamol	PEG 6000,PVP	[18]
Mebendazole	PEG6000,PVA	[33]
Tranilast	PEG 6000 EC 50000	[34]
Felodipine	PEG 6000 HPMC SSG CP CS	[35]
Carbamazepine	PVP, HPMC	[36]
Glibenclamide	PEG6000, HPMC, E50 LV	[38]
Tolbutamide	Hydroxypropylcellulose	[39]

METHODS OF PREPARATION OF DRUG AGGLOMERATES

1) Quasi-emulsion solvent diffusion method[19]

The quasi-emulsion solvent diffusion (QESD) was first mentioned in 1989 by Kawashima and co- workers. This method involves the interactions between the drug and the good solvent are stronger than the interactions between the good solvent and the poor solvent. The drug is dissolved in the good solvent and when the solution is dispersed into the poor solvent, fine droplet are created, even though good and poor solvents are miscible. Formation of an unstable emulsion is take placed by the increase in interfacial tensions between both solvents. The good solvent slowly spread out of the emulsion droplets into the outer poor solvent phase, and the poor solvent spread into droplets, which reduces the solubility and eventually

causes drug crystallization inside the droplets. Residual good solvent in the droplets acts as a bridging liquid to agglomerate the generated crystals.

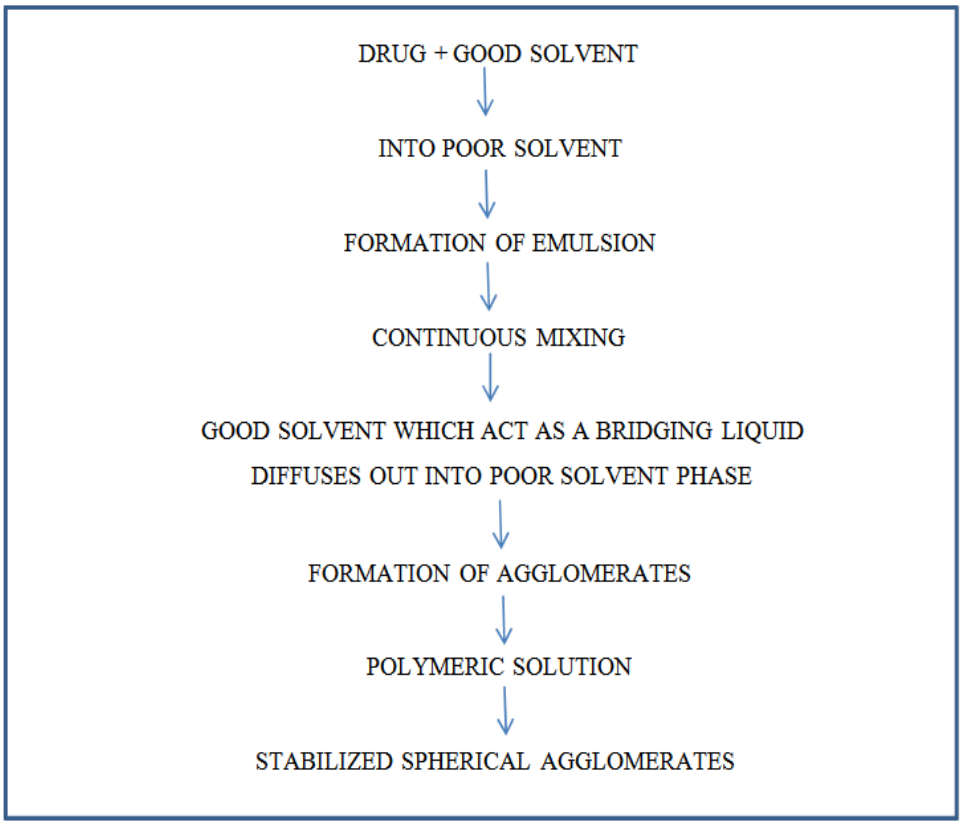

Figure 2: Steps involved in Quasi-emulsion solvent diffusion method.

2) Ammonia diffusion method

This is a modified spherical crystallization technique applicable to amphoteric substances, which are only soluble in acidic or alkaline aqueous solutions and insoluble in neutral aqueous solutions or organic solvents. In this technique, an aqueous ammonia solution is used as the good solvent and it also acts as a bridging liquid.[20] The poor solvent is selected on the basis of the drug solubility in that solvent and good miscibility with ammonia and water. Water-immiscible solvents such as hydrocarbons or halogenated hydrocarbons are a third component in the system, inducing liberation of the ammonia.[20,21] The drug is dissolved in an aqueous ammonia solution and poured into a mixture of a poor solvent and a water-immiscible solvent. It is assumed that the poor solvent enters the droplets of aqueous ammonia solution and causes drug precipitation without forming ammonium salts. Simultaneously, the ammonia diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker, which then determines the final size of agglomerates. It is important to find a suitable combination of solvents in order to attain a high crystallization

rate. When too much immiscible or poor solvent is applied, the resultant agglomerates form a large solid mass or a paste and with too little solvent, drug crystals form without agglomeration.

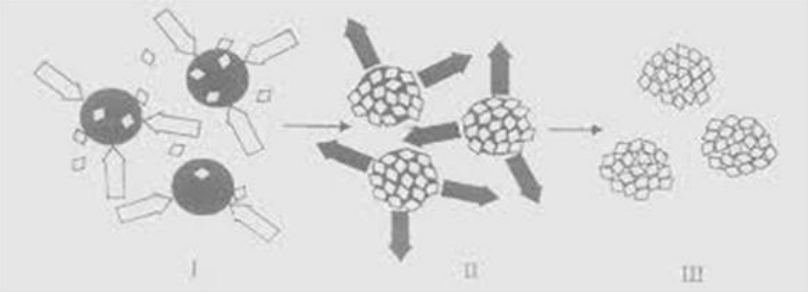

Figure 3: Steps involved in Ammonia diffusion method.

First, the drug dissolved in ammonia water is precipitated while the droplets collect the crystals (Figure I). Simultaneously, ammonia in the agglomerate diffuses to the outer organic solvent (Figure II). Its ability to act as a bridging liquid weakens and subsequently spherical agglomerates are formed (Figure III).

3) Neutralization Method

This technique involves the formation of fine crystals by neutralization and consequently their agglomeration by a bridging liquid. The drug was dissolved in alkaline solution and then poured into an acidic solution containing polymers and bridging liquid under constant agitation. The drug crystals are precipitated out by neutralization of the base with acid. Then the precipitated crystals were simultaneously agglomerated with the incorporated polymer through the wetting action of the bridging liquid.[22]

4) Solvent change method: This method is not applicable to water insoluble drugs.

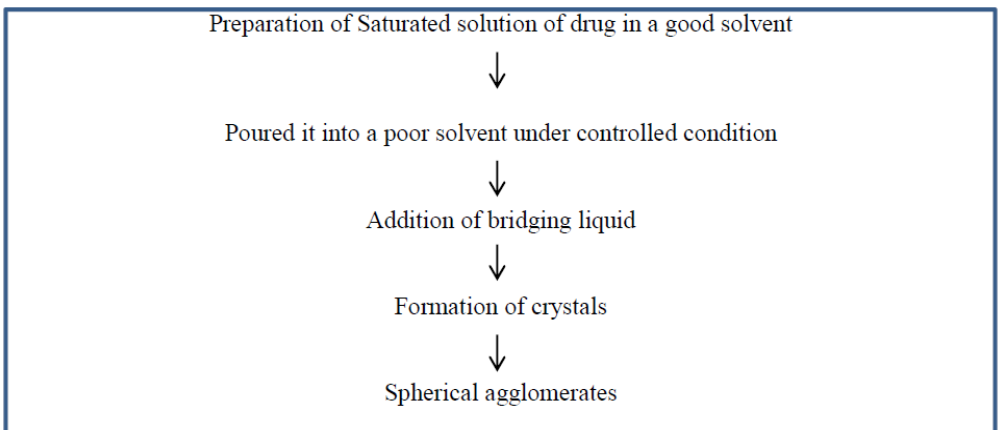

Figure 4: Steps involved in Solvent change method.

Due to discriptive forces stirring rate is inversely proportional to agglomeration. Porosity of agglomeration decreases with the increase in the concentration of solid.

Crystal-co-agglomeration technique (CCA)

It is a modification of the spherical crystallization technique in which drug is crystallized and agglomerated with an excipient or with another drug. This process enables design of agglomerates containing two drugs or poorly compressible drug in combination with diluents and is restricted to water insoluble large-dose drugs only. Difference in the physicochemical properties of drug molecules and excipient is a major challenge in the selection of the solvent system for the Crystal- co-agglomeration technique.

Table 1: Gives List of Various Solvent Used By Researchers For Preparation Of Sa Of Different Drugs.

Drug	Solubility of drug(api)for compression	Soluble in good solvent	Insoluble in(bad solvent)	Bridging liquid	Technique used for preparation of SA	Reported improved micromeritic properties	Reference
Antibiotics							
Ampicillin trihydrate	Flowabilit y and compressib ility	Amm. water	acetone	DCM	SC	TD:0.27 BD:0.15 Ɵ:22.5 CC:8.2	[6]
Cefuroxim e axetil	Solubility, dissolution rate	acetone	water	DCM	QESD	55% in 45 min	[7]
Enoxacin	Flowabilit y and compressib ility	Amm. water	acetone	Amm. water	ADM	TD:0.30 BD:0.18 Ɵ:25.3 CC:7.3	[8]
Norfloxaci n	Flowabilit y and compressib ility	Amm. water	acetone	Amm. water	ADM	TD:0.87 BD:0.26 Ɵ:19.8 CC:6.84	[9]
Roxythrom ycin	Flowabilit y and compressib ility	methanol	water	chloroform	SC	TD:0.54 BD:0.74 Ɵ:23.2 CC:8.2	[10]
NSAIDS]							
Aceclofena c	Solubility, dissolution rate, micromerit ic property	acetone	water	DCM	SC	TD:0.78 BD:0.54 Ɵ:23.7 CC:6.2	[11]
Aspirin	Flow property	Acid buffer	methanol	Chloro for m	SC	TD:0.85 BD:095	[12]

						Θ:29.2 CC:7.6	
Acetyl salysylic acid	Flowabilit y and compressib ility	ethanol	water	Carbon tetrachlori de	SC	TD:0.78 BD:0.87 Θ:17.8 CC:8.5	[13]
celocoxid	Solubility, dissolution rate, micromerit c property	acetone	water	Chlorofor m	SC	TD:0.95 BD:0.89 Θ:26.8 CC:8.6	[14]
fenbufen	Flowabilit y and compressib ility	THF	water	Isi propyl acetate	SC	TD:0.87 BD:0.65 Θ:29.3 CC:8.6	[15]
Flubiprofe n	Flowabilit y and compressib ility	acetone	water	hexane	SC	TD:0.45 BD:0.65 Θ:27.3 CC:7.2	[16]
Ibuprofen	Flowabilit y and compressib ility	Ethanol	water	ethanol	SC	TD:0.54 BD:0.78 Θ:28.9 CC:8.6	[17]
ib- paracetam ol	Flowabilit y and compressib ility, Dissol ution behavior	DCM	water	DCM	CCA	TD:0.56 BD:0.87 Θ:25.8 CC:7.6	[18]
ibuprofen	Flowabilit y and compressib ility	DCM	water	DCM	CCA	TD:0.78 BD:0.65 Θ:18.5 CC:9.6	[19]
Indometha cin	Flowabilit y and compressib ility	Dimethyl formide	water	Chlorofor m	SC	TD:0.45 BD:0.64	[20]

						Θ:24.8 CC:9.32	
Ind.mepiri zole	Flowabilit y and compressib ility	Ethyl acetate	water	chloroform	CCA	TD:0.54 BD:085 Θ:28.2 CC:5.2	[21]
Ketoprofen	Micromeritic property, dissolutionrate	Isopropy l acetate	water	Chlorofor m	CCA	TD; 0.20 BD; 0.18 Θ: 21.16 CC: 9.09 HR: 1.100	[22]
Mefenamic acid	Flowability wettability compressibility	Amm. water	acetone	Amm. water	ADM	TD:0.87 BD:0.25 Θ:27.5 CC:6.87	[24]
Naproxane	Flowability, compressib ility	acetone	water	Chlorofor m	SC	TD; 0.27 BD; 0.25 Θ: 35.6 CC: 7.5 HR: 1.23	[25]
Nabumeto ne	Flowability and compressib ility	ethanol	water	cyclohexane	SC	TD; 0.87 BD; 0.65 Θ: 28.6 CC: 7.4 HR:2.4	[26]
Piroxicam	Flowability and compressib ility	NaOH	water	Chloro for m	SC	TD:0.78 BD:0.62 Θ:22.6 CC:8.9	[26]
Propylphe nazone	Flowability and compressib ility	Ethyl acetate	water	Isopropyl acetate	SC	TD:0.72 BD:0.37 Θ:28.2	[27]

						CC:9.5	
Bronchodilators							
aminophyll ine	Flowabilit y and compressib ility	ethanol	water	chloroform	SC	TD:048 BD:0.37 ϴ:30.8 CC:4.8	[31]
theophyllin e	Flowabilit y and compressib ility	ethanol	NaCL	water	SC	TD:0.38 BD:0.77 ϴ:28.4 CC:8.1	[32]
Antifungal							
gresiofulvi n	Flowabilit y and compressib ility	DCM	Water	DCM	QESD	CC:14.75 ϴ:22 HR:1.12	[30]
Antiepileptic							
Carbamaze pine	Flowabilit y and compressib ility	ethanol	water	chloroform	QESD	TD: 0.25 ϴ:19.1 HR:1.8	[37]
Antihypertensi ve							
felodipine	Dissolutio n rate	acetone	water	DCM	QESD	98.83% in 120 min	[35]
Antiallerg ic							
tranilast	Flowabilit y and compressib ility	acetone	water	DCM	SC	TD:0.95 BD:0.47 ϴ:29.3 CC:8.4	[34]
Antihelmintic							
Mebendaz ole	Poor flow properties, segragatio n tendency ,poor compressib	acetone	water	hexane	SC	BD;0.95 TD;0.301 CC;24.90 HR;1.33	[33]

	ility						
B-adrenergic blokers							
Acebutalol HCL	Flowabilit y and compressib ility	ethanol	water	Isopropyl acetate	QESD	TD:0.78 BD:0.46 Θ:27.6 CC:7.4	[37]
Antidiabetic							
glibenclam ide	Flowabilit y and compressibility	DCM	water	chloroform	SC	CC:20.86 BD:0.91 TD:1.15 Θ:30.2 HR:1.26	[38]
tolbutamid e	Flowabilit y and compressibility	ethanol	water	Isopropyl acetate	QESD	TD:0.38 BD:0.65 Θ:30.4 CC:12.5	[39]
Other							
Ascorbic acid	Flowability, compactab ility	water	Ethyl acetate	Ethyl acetate	SC,QESD	TD:0.79 BD:0.35 Θ:32.9 CC:8.3	[41]
Aspartic acid	Flowabilit y and compressib ility	methanol	water	chloroform	SC	BD;0.51 TD:0.82 CC:26.41 Θ:24.63	[42]
Benzoic acid	Particle properties	ethanol	water	chloroform	SC	TD:0.95 BD:0.45 Θ:29.7 CC:11.8	[43]
Bromohex ane HCL	Poor compressib ility, poor release	DCM	water	DCM	CCA	TD; 0.95 BD; 0.97	[44]

	rate					Θ: 26.82 CC: 2.06 HR: 1.03	
valsartan	Flowability, compressib ility	Acetone	water	chloroform	SC	CC;7 HR;1.08 Θ;30..96	[45]
Key words: SA = Spherical Agglomeration, ADS = Ammonia Diffusion System, CCA = Crystal- co-agglomeration technique, SC=Solvent change method, QESD= quasi-emulsion solvent diffusion TD- Tapped Density, BD- Bulk Density, Θ- Angle of Repose, CC-Carrs Compressibility, HR- Housners ratio.							

EVALUATION OF DRUG AGGLOMERATES

1) Drug content estimation

The weighed quantity of spherical agglomerates is taken and triturated in distilled water. This solution is mixed with methanol and phosphate buffer solution (PBS) of pH 6.2 to produce 100 ml. Absorbance is measured using UV spectrophotometric method and drug content is estimated.[4]

2) Solubility analysis

The required quantity of spherical agglomerates were dispersed in distilled water in a screw capped glass vials. The vials is then shaken for two hours in a mechanical shaker. The concentration of drug is determined by UV spectrophotometric method at higher wavelength.

3) Particle shape and surface morphology

The surface topography type of crystals (polymorphism and crystal habit) of the spherical agglomerates are analyzed by using scanning electron microscopy.

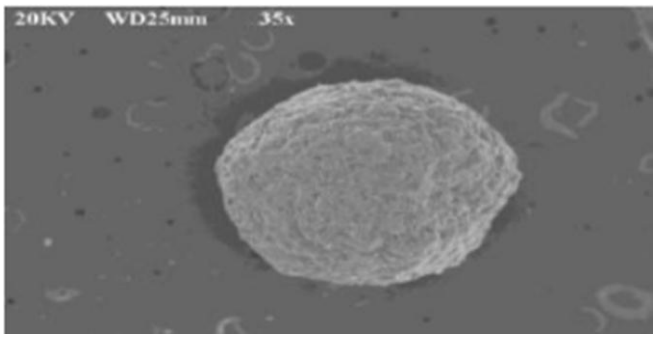

Figure 4: A representation of SEM image of spherical agglomerates by using polymer.[17]

4) X-ray powder diffraction

X-ray powder diffraction Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound. The form of crystals in agglomerates is determined by using X-ray powder diffraction technique. This is an important technique for establishing batch-to-batch variation of a crystalline form.

5) Determination of micromeritic properties

The bulk density, tapped density, Hausner's ratio and angle of repose is measured and calculated for the developed spherical agglomerates.

6) Carr's compressibility index

A volume of powder is filled intoa graduated glass cylinder and repeatedly tapped for a known duration. the volume of powder after tapping is measure.

Table 3: Relationship between carr's index and flow character.

Flow character	Carr's index(%)
Excellent flow	5-15
good	16-18
fair	19-21
poor	22-35
Very poor	36-40
Extremely poor	>40

7) The angle of repose

The sample is poured onto the horizontal surface and the angle of the resulting pyramid is measured. it is the maximum angle possible between the surface of a pile of the powder and the horizontal plane.it is given by the equation:

$\tan \Theta = h/r$

Were-

h- height of the pile

r- radius of the base of the pile. Θ- Angle of repose.

Table 4: Relationship between flow property and angle of repose.

Flow property	Angle of repose(0°)
Excellent	25-30
Good	31-35
Fair	36-40
Poor	41-45
Very poor	46-55
Extremely poor	>66

8) Solubility analysis

The required quantity of spherical agglomerates are dispersed in distilled water in a screw capped glass vials. The vial is then shaken for two hours on a mechanical shaker. The concentration of drug is determined by UV spectrophotometric method at maximum wavelength.

9) Differential Scanning Colorimetry

Differential scanning colorimetry spectra of pure drug, polymers and optimized agglomerates are recorded using Differential scanning colorimeter. it is useful in drug excipient interaction studies.

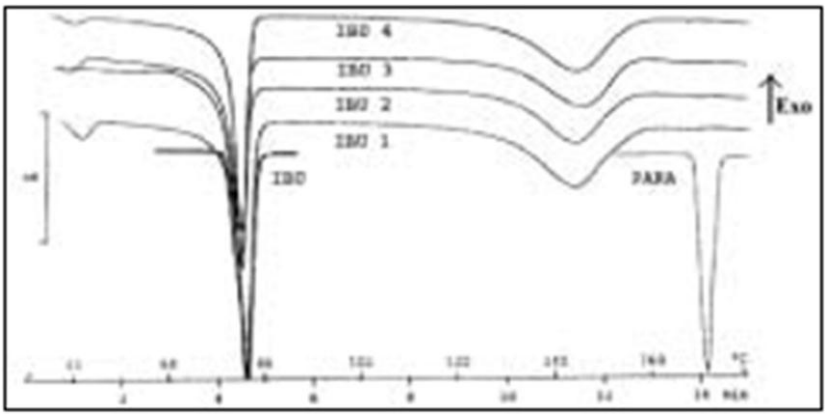

Fig no 5: Representation of DSC thermograms of ibuprofen, paracetamol and their agglomerates.[18]

10) Fourier transform infra-red spectroscopy

Infrared spectra of pure drug and prepared agglomerates can be recorded using Infrared spectrophotometer.

11) Contact Angle Determination

Agglomerates were compacted at tons of pressure by using a hydraulic press for 1 minute of dwell time. A drop of water (50 µL) was placed on the compact by using a micropipette. A photograph of the placed drop is taken to measure the contact angle.

12) In Vitro Dissolution

Agglomerate directly affect absorption kinetics and bioavailability. Various Official dissolution apparatus is used for determination of dissolution rate and bioavaibility.

CONCLUSION

CCA techanique provide shorter the manufacturing process and reduces the cost, it required less machinery. micromeritic and physico-chemical properties of the drug is improved by this technique. the drug agglomerates is very usefull for direct compression. it reduces number of steps with compared to conventional granulation techniques. various polymers can be used in this process.

FUTURE PROSPECTS

The agglomerates obtained by SA can act as a matrix beads due to uniform distribution of Spherical crystallized drug at the surface of diluent. Agglomerates of plain excipients or diluents can be prepared and used as a placebo therapy. The intact agglomerates can be given in the form of encapsulated dosage form. Simultaneously, agglomerates having different drug release profiles can be prepared. Smart selection of polymers and diluents can extend the release of drug or can improve dissolution of poorly soluble drugs.

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