Spherical Crystallization of Dapsone To Improve Physicochemical and Micromeritics Properties.

1*Shrutika Yashwant Patil, 2*Shweta Ramesh Nikam, 3*Dipak Jayappa Kare

1* B.Pharmacy student of Nootan College of Pharmacy, Sangli

2* B.Pharmacy student of Nootan College of Pharmacy, Sangli

3* Assistant professor of Nootan College of Pharmacy, Sangli

Abstract :

In 1986, Kawashima pioneered the spherical crystallization technique for enlarging the size of drugs in the field of pharmacy. This innovative approach aimed to enhance the flow and compressibility characteristics of microcrystalline drug candidates. The process of spherical crystallization involves utilizing agglomerating solvents, quasi-emulsion solvent diffusion, and ammonia diffusion techniques. Optimization of temperature and agitation speed is crucial to achieve spherical agglomerates within the desired range, which is essential for improving compressibility. The resulting spherically agglomerated crystals can be directly prepared into tablet form or compounded into pharmaceutical systems without the need for additional processing such as granulation. Spherical crystallization serves as a particle design technique, enabling simultaneous crystallization and agglomeration in a single step. It has proven effective in enhancing the flowability and compatibility of crystalline drugs. Characterization of spherical crystals typically involves Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD) to assess any physicochemical interactions between the drug and carrier that could impact dissolution. Additionally, the solubility of the crystals is evaluated to ascertain their performance.

Key words :

Flowability, Compatibility, Agglomeration, Spherical Crystallization, Direct Compression, Physicochemical properties.

Introduction :

Spherical crystallization of Dapsone, also known as Crystallo-co-agglomeration, is a specialized technique used in pharmaceutical formulation to enhance drug properties such as solubility, dissolution rate, and bioavailability. In this process, Dapsone crystals are transformed into spherical agglomerates through the use of a bridging liquid or binder solution, leading to improved flow properties and compressibility. These spherical agglomerates offer advantages in terms of uniformity, stability, and ease of handling during tablet manufacturing.

Regarding tablet formulations, Dapsone is commonly formulated as oral tablets for the treatment of various dermatological conditions such as leprosy and dermatitis herpetiformis. Formulation considerations include selecting appropriate excipients to optimize drug release, stability, and patient acceptability. Excipients like diluents, binders, disintegrants, and lubricants play crucial roles in ensuring the tablet's quality attributes.

Research in this area might focus on optimizing the spherical crystallization process parameters, such as solvent selection, temperature, and agitation speed, to achieve desired drug particle characteristics. Additionally, investigating the impact of different tablet formulation variables on drug release kinetics, stability, and bioavailability can provide valuable insights for the development of improved Dapsone tablet formulations.

Tablets are a predominant form of oral drug delivery, constituting over 50% of such systems and 70% of pharmaceutical preparations. Direct tableting, a modern manufacturing method, involves mixing and compressing powders, yielding benefits in time, cost, and energy. However, achieving good micrometric properties, like followability, is crucial for compressing drugs directly. Needle-shaped or plate-shaped crystals pose challenges due to poor followability. To address this, Kawashima introduced spherical crystallization, enlarging particle size during crystallization to produce dense, spherical agglomerates suitable for direct tableting. Initially demonstrated using silica sand and calcium chloride, this technique evolved to encompass drug particles, enabling control over crystal type and size. Spherical crystallization simultaneously conducts crystallization and agglomeration, transforming crystals directly into compact, spherical forms. It's a pivotal particle engineering technique, enhancing followability, solubility, and compatibility. Agglomeration, central to this process, involves merging smaller crystals into larger particles.

Need of Spherical Crystallization process:

Developing innovative strategies to enhance the bioavailability of drugs with inherently poor aqueous solubility poses a significant challenge in formulating solid dosage forms. Traditional methods such as mechanical mercerization of crystalline drugs and the inclusion of surfactants during crystallization are commonly employed but can introduce formulation complexities. Mercerization alters the flow and compressibility of crystalline powders, while the addition of surfactants often yields modest improvements in aqueous solubility. Addressing these challenges, Kawashima pioneered a spherical crystallization technique, effectively enhancing the flow and direct compressibility of numerous microcrystalline drugs.

Advantages of spherical crystallization process

1. **Improved flow properties:** Spherical crystallization transforms irregularly shaped crystals into spherical agglomerates, enhancing flowability and reducing issues such as caking and segregation during processing.

2. **Increased compressibility:** The spherical agglomerates have better compressibility compared to irregular crystals, leading to improved tabletability and uniform tablet weight.

3. **Enhanced dissolution rate:** Spherical crystallization can improve the dissolution rate of poorly soluble drugs by increasing the surface area available for dissolution.

4. **Uniform particle size distribution:** This technique produces particles with a narrower size distribution, leading to more consistent drug release profiles and dosage uniformity.

5. **Better stability:** Spherical agglomerates often exhibit improved stability due to reduced surface area and decreased susceptibility to environmental factors such as moisture and light.

Disadvantages:

1. **Process complexity:** Spherical crystallization involves multiple steps and parameters, including solvent selection, temperature control, and agitation speed, which can make the process more complex and time-consuming.

2. **Equipment requirements:** Specialized equipment such as high-speed mixers or fluidized bed processors may be required for spherical crystallization, increasing the initial investment and operating costs.

3. **Potential for polymorphism:** Changes in crystalline form during the spherical crystallization process may lead to polymorphism, which can affect drug stability and bioavailability.

4. **Limited applicability:** Spherical crystallization may not be suitable for all drug substances, especially those with certain chemical properties or solubility characteristics.

5. **Scale-up challenges:** Scaling up spherical crystallization from laboratory to commercial production may pose challenges in maintaining process robustness and product consistency.

Techniques of spherical Crystallization

There are several techniques of spherical crystallization

1) Cooling crystallization technique
2) Steering crystallization technique
3) Solvent change method
4) Emulsion solvent diffusion
5) Ammonia solvent diffusion
6) Neutralization techniques
7) Crystalloid co agglomeration

1) **Cooling Crystallization technique:**

In this type of crystallization, the liquid which is to be crystallized, is cooled to such temperature which is below the equilibrium solubility is usually when the temperature increase, the solubility of a liquid also increases, so when it is cooled to the temperature that is below the equilibrium solubility, it forms crystals.
Procedure:

The procedure for the cooling spherical crystallization technique of Dapsone involves the following steps:
1 . Preparation of Dapsone Solution: Dissolve Dapsone in a suitable solvent, such as ethanol or methanol, to form a clear solution with a concentration above its solubility limit at the desired temperature.
2.Cooling the Solution: Gradually cool the Dapsone solution to a temperature below its solubility limit, typically by placing the solution in an ice bath or using a temperature controlled cooling apparatus.
3.Nucleation: As the temperature decreases, nucleation of Dapsone crystals will occur. This nucleation process can be initiated by seeding the solution with small Dapsone crystals or allowing spontaneous nucleation to take place.
4.Crystal Growth: Once nucleation occurs, allow the Dapsone crystals to grow by maintaining the solution at the desired temperature for a specific duration. Controlled crystal growth will lead to the formation of larger, well-defined crystals.
5.Separation and Washing: After sufficient crystal growth, separate the Dapsone crystals from the solution using techniques such as filtration or centrifugation. Wash the crystals with a suitable solvent to remove any impurities or residual solvent.
6.Drying: Dry the Dapsone crystals to remove any remaining solvent and ensure the crystals

are free- flowing and stable. This can be achieved by air drying, vacuum drying, or using other drying techniques.

2) **Starring crystallization Technique**

Procedure:

The procedure for the continuous stirring process of spherical crystallization involves the Following steps :-

1 .Preparation of Drug Solution: Dissolve the drug in a suitable solvent to form a clear Solution.

2. Addition of Anti-solvent: Gradually add an anti-solvent (such as water or a nonsolvent for The drug) to the drug solution under constant stirring.
3. Controlled Agitation: Maintain a controlled stirring speed to ensure uniform mixing of the Drug solution and anti-solvent.
4. Nucleation and Crystal Growth: As the anti-solvent is added, nucleation occurs, leading to

The formation of small drug crystals. These crystals continue to grow due to supersaturating Of the drug in the solution.

5. Spherical Particle Formation: The continuous stirring and controlled addition of antisolvent Facilitate the formation of spherical drug particles with controlled properties.
6. Separation and Drying: After the desired particle size and morphology are achieved, Separate the spherical crystals from the suspension and dry them using suitable methods Such as filtration and drying under vacuum.
7. Characterization: Finally, characterize the spherical crystals for their size, shape, surface Properties, and drug content to ensure quality and reproducibility. This process allows for The production of spherical drug particles with enhanced properties, suitable for improving Drug solubility, dissolution rate, and bioavailability.

Formulation Table :

Sr. No.	Formulation	Chloroform (ml)	Diethyl ether (ml)	PVP (gm)	Drug (gm)
1	F1	5	10	1	1
2	F2	10	10	1	1
3	F3	15	15	2	2
4	F4	20	15	2	2
5	F5	25	15	2	2

Table No :1

Evolution Parameter of Spherical Crystallization :

Dissolution test

The dissolution test for spherical crystallization tablets typically involves assessing the release of the active ingredient over a specified time period. The standard range can vary depending on factors like the drug's characteristics, intended use, and regulatory requirements. Generally, dissolution testing may span from 30 minutes

to 2 hours, with sampling intervals at regular time points. However, the specifics should align with regulatory guidelines and product specifications.

Disintegration Test

In simple way disintegration test is a process in which solutes dissolve in a solvent. This test determines whether dosage forms disintegrate within a prescribed time i. e. disintegration time when placed in a liquid medium under the prescribed experimental conditions of various dosage forms such as tablets, capsules and suppositories. Disintegration is a process of breaking down a substance into small/tiny fragments to improve its solubility in a solvent also it is used to check how much drug is soluble in The disintegration test standard limits for spherical crystallization tablets of Dapsone typically adhere to the guidelines provided by pharmacopoeias such as the United States Pharmacopeia (USP) or the European Pharmacopoeia (Ph. Eur.). These standards ensure that the tablets disintegrate within a specified time frame, usually around 15 to 30 minutes, when tested under specified conditions. However, the exact limits may vary depending on the formulation and intended use of the tablet.

Weight Variation test :

Twenty tablets were selected randomly from the formulation. Tablets were weighed one by one And then the average weight was calculated. Deviation of each tablet from average weight was Calculated and then the per cent deviation was computed.

The formula for weight variation is

Weight Variation = (Iw – Aw)/Aw x 100%

Where is the individual weight of a tablet and Aw is the average weight of the tablet.

The result of the weight variation test is expressed as a percentage.

The limits usually specify a maximum percentage difference in weight between individual tablets, typically around ±5% or ±7.5% of the average weight of the tablets in the batch, depending on the pharmacopoeial guidelines and the dosage form.

Friability Test :

Friability testing is used to test the durability, crushing strength, capping & lamination of Tablets before and after to packing processes and during a transit. Dropping a sample of tablets over a fixed time repeatedly involves in it. By using a rotating drum with a baffle attached on it. The result is inspected for broken tablets, and the percentage of tablet mass lost through chipping is

Calculated by using following formula;

Friability of Sample = (Wi – Wf) Wi * 100

Standard limit of friability test is no more than 1 %

Hardness test :

It matches with friability testing but they are not the same thing. The breaking point of a tablet is
Based on its shape so it is mainly performed on tablets to find out how it changes under different Conditions of storage, transportation, packaging and handling before usage. So, we can say that it Is a laboratory technique used

by the pharmaceutical industry to determine the breaking point and Structural integrity of a tablet. Standard range of hardness test is 4-6 Kg / cm2

Evolution of granules :

Evaluation parameters angle of repose, tapped density, bulk density, Carr's Index and

Hausner's Ratio were carried out for the granules that are showed in the Table No 2

Sr. No	**Formulation parameter**	**F1**	**F2**
1	Angle of repose (o)	34.6	35.4
2	Bulk density (g/ ml)	1.96 (g/ml)	1.90 (g/ml)
3	Tapped Density (g/ ml)	2.3 (g/ml)	2.2 (g/ml)
4	Carr's index	12	11.8
5	Hausner's Ratio	1.17	1.15

Table no. 02

Evolution of tablet :

The evaluation parameters like Physical appearance, weight variation, friability, hardness, Thickness and disintegration test were carried for the batches and some of them are in table no 3

Sr. No	**Evolution parameter**	**F1**	**F2**
1	Hardness (kg/ cm2)	7	6.9
2	Weight variation%	3	4
3	Friability%	0.5	0.4

4	Disintegration test (min)	2.26 (min)	2 (min)

Table no. 03

Evolution of spherical crystallization :

Formulation	**Drug (gm)**	**Chloroform (ml)**	**PVP (gm)**	**Diethyl Ether**	**Final product**
F1	1	5	1	10	Slightly
F2	1	10	1	10	Average
F3	2	15	1	10	Medium
F4	2	20	1	10	High
F5	2	25	2	10	Very high

Table no. 04

Calibration Curve :

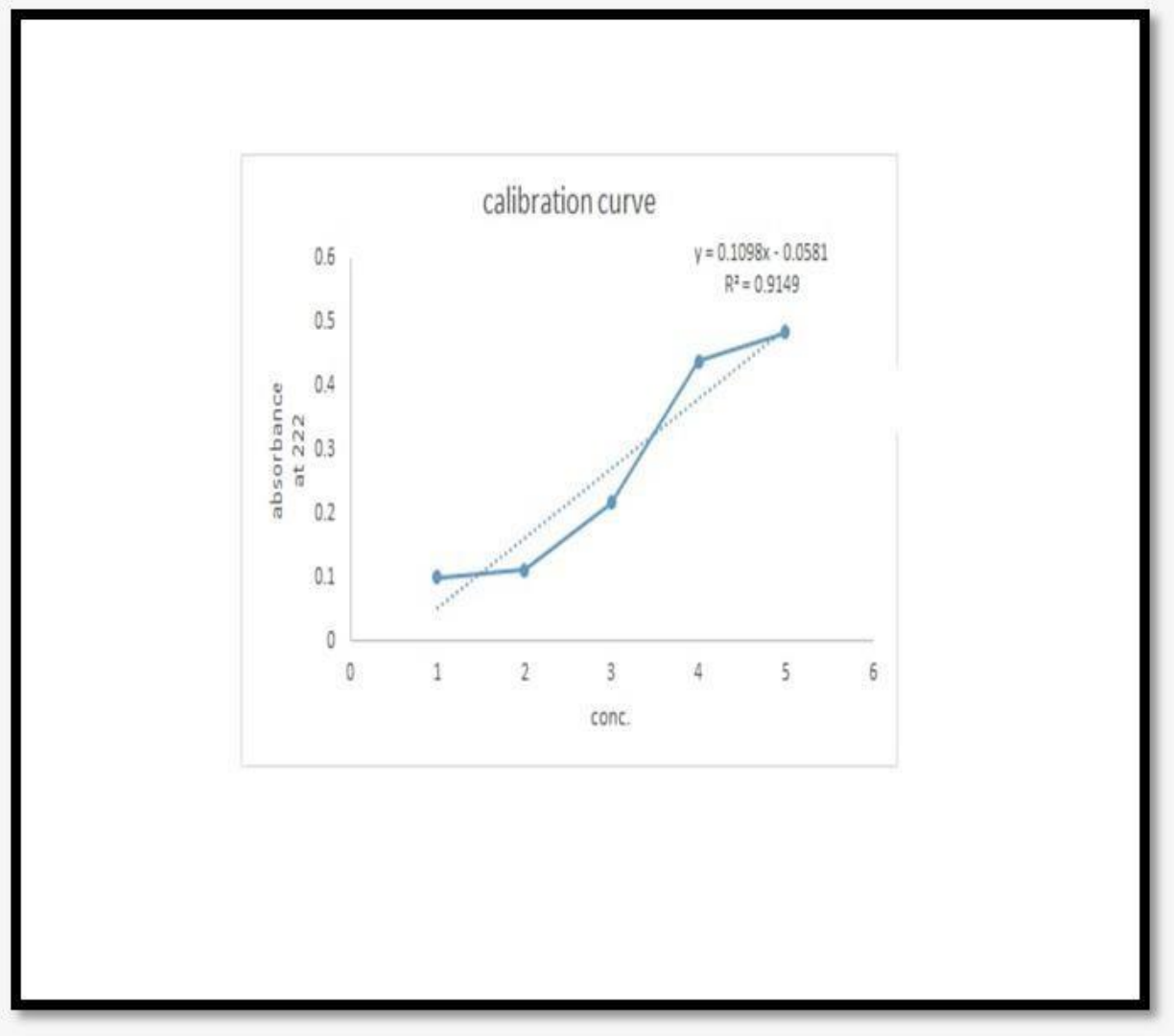


Figure no. 01

IR of Dapsone Granules :

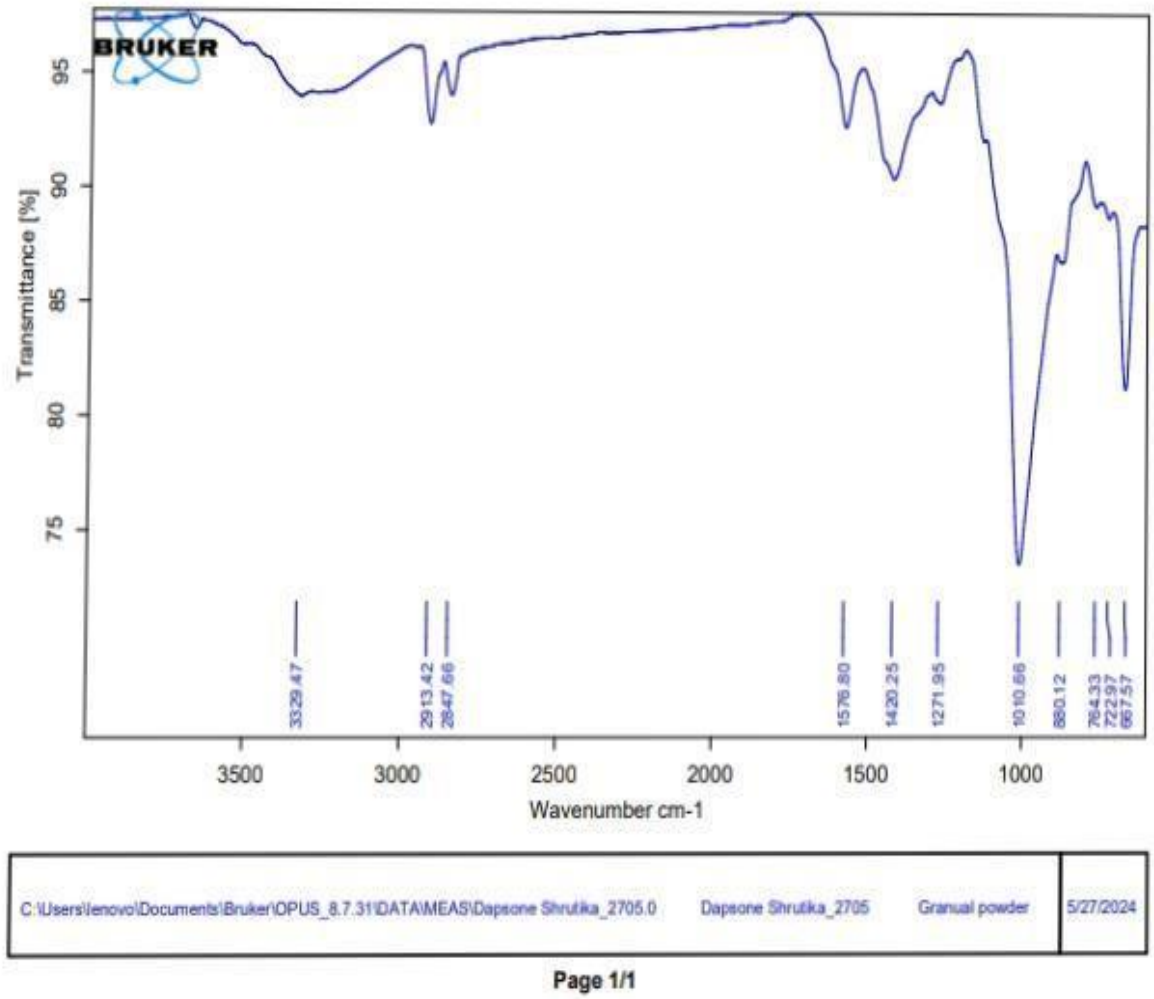
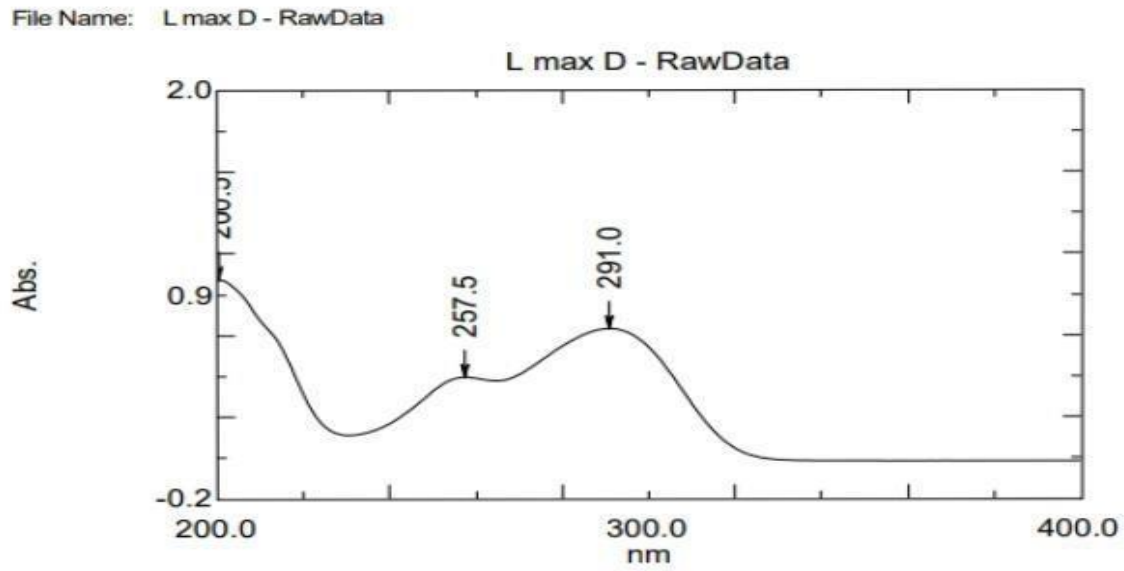


Figure no. 02

Uv L (Max) of drug sample :



[Summary]

Data Information	
Data is:	Measurement Data
Data Set Name:	RawData
Sample Name:	Dapsone
Sample ID:	
Option:	
Analyst:	Anjali
Date/Time:	27-05-2024 01:11:32 PM
Comments:	
Parameter File Name:	E:\Anjali C. Bawadekar\NCP\L. max _Dapsone.vspm
Report File Name:	
Software Information	
Software Name:	LabSolutions UV-Vis
Version:	1.14
Instrument Information	
Instrument Name:	UV-Visw Spectrophotometer
Instrument Type:	UV-1900 Series
Model (S/N):	UV-1900i (A12536183998)

[Measurement Parameters]

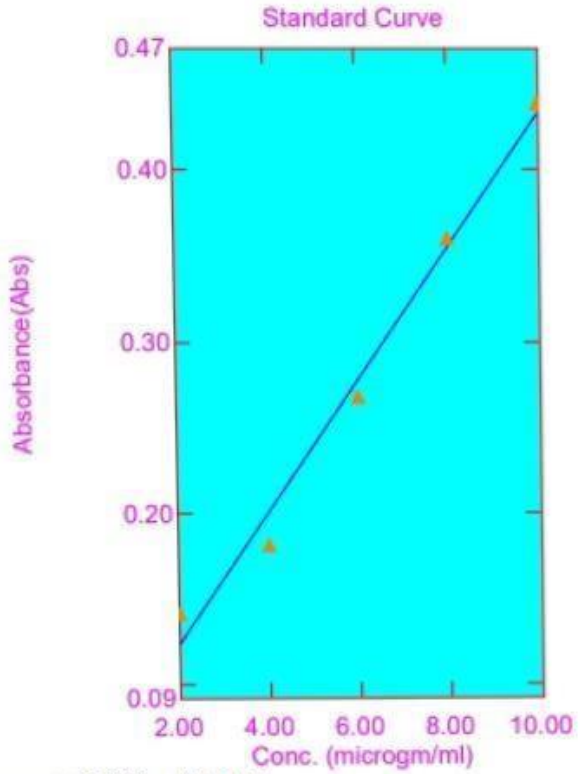
[Measurement]	
Start:	400 nm
End:	200 nm
Data Interval:	0.5 nm
Scan Speed:	Medium speed
Spectrum Type:	Absorbance
[Accessories]	
Accessories:	None
[Advanced]	
Slit Width:	1.0 nm
Light Source Switch Wavelength:	340.00 nm
S/R Switch:	Standard
[Repeat]	
Repeat Measurement:	OFF
[Post-processing]	
Spectrum Transformation:	OFF
Data Processing Table:	OFF
Print:	OFF

Figure no. 03

Cc of Dapsone powder

Quantitation Standard Table

Print Date : 27-05-2024 01:28:46 PM



y = 0.0385986 x + 0.0464966
r2 = 0.98615
r(m)2 = 0.98615

[Summary]

File Information

Filename:	C:\UVVis-Data\Data\CC_ dapsone.vqud
Parameter File Name:	E:\Anjali C. Bawadekar\NCP\Cc_ Dapsone.vqum
Analyst:	Anjali
Date/Time:	27-05-2024 01:27:59 PM
Comments:	
Report File Name:	

[Measurement Parameters]

[Wavelengths]	[St
Type of Measuring Mode:	Absorbance
rounded:	OFF
Column Name:	WL257.5
Measuring Method:	Point (257.50nm)
Column Name:	WL291.0
Measuring Method:	Point (291.00nm)
[Calibration Curve]	-----
Calibration Curve Creation:	Sample Measurement
Calculation Method:	1.0000 * WL257.5
Column Name:	Result
Calibration Curve Formula:	Calculated Value = K1 * Concentration + K0
Pass Origin:	OFF
Unit of Concentration:	microgm/ml
Pass/Fail Judgment:	OFF

[Standard Table]

	Sample Name	Date	Time	Conc	WL257.5	WL291.0	Result
1	0.2 ml	27-05-2024	01:21:38 PM	2.000	0.142	0.160	0.1
2	0.4 ml	27-05-2024	01:23:32 PM	4.000	0.182	0.276	0.1
3	0.6 ml	27-05-2024	01:25:13 PM	6.000	0.268	0.408	0.2
4	0.8 ml	27-05-2024	01:26:31 PM	8.000	0.360	0.558	0.3
5	1 ml	27-05-2024	01:27:27 PM	10.000	0.438	0.686	0.4

Figure no. 04

Result and Discussion ;

The formulation was prepared by wet granulation method were tested for Preformulation studies for the effective evaluation of tablets. All the evaluated Preformulation parameters are shown in table 3.Based on the pre-formulation study the Flow property of granules was good. The physical parameters of compressed tablets were Shown in table 2. The compressed tablets color was Light brown color. The weight Variation test, hardness, thickness, friability and disintegration time. Was successfully performed.

Conclusion :

In conclusion, the project work on spherical crystallization of Dapsone tablets has Demonstrated significant promise in enhancing the pharmaceutical properties of the drug. Through this innovative approach, we have achieved improved drug dissolution, Enhanced stability, controlled release kinetics, uniform particle size distribution, and Compatibility with various excipients. These advancements not only hold potential for Cost- effective manufacturing at scale but also offer tangible benefits for patient Compliance and therapeutic outcomes. Overall, the successful implementation of Spherical crystallization underscores its value as a viable strategy for optimizing the Formulation and performance of Dapsone tablets, thus paving the way for further Exploration and development in pharmaceutical research and production. The spherical
Crystallization study on Dapsone indicates its efficacy in enhancing the drug's solubility, Dissolution rate, and ultimately its bioavailability, suggesting its potential as a viable Method for improving therapeutic outcomes.

Reference :

1) Maghsoodi M. Role of solvents in improvement of dissolution Rate of drugs: crystal habit and crystal agglomeration. Adv Pharm Bull 2014;1:1-6.

2) Ujwala R, Redasani K, Kothwade S. Preparation and in-vitro Evaluation of loperamide hydrochloride spherical crystals by Emulsion solvent diffusion technique. Int J Pharm Pharm Sci 2013;5:409-13.

3) Krishna E, Gupta V, Jyothi S. Spherical crystallization-a modern Technique for direct compression of pharmaceutical Substances. Asian J Pharm Clin Res 2012;5:114-

4) Dixit M, Kulkarni P, Johri A. Spherical agglomerates of Mefanamic acid by solvent change method. Int J Pharm Sci2011;2:111-25.

5) Parida R. Evaluation parameters for spherical agglomerates formed by spherical Crystallization technique. Int J Pharma Bio Sci 2010;1:1-10.

6) Yadav VB, Yadav AV. Comparative tabletting behaviour of crystals granules with Spherical agglomerated crystals prepared by spherical crystallization technique. Int J ChemTech Res2009;1:476-82.

7) S. R. Shah, M. M. Patel, "Spherical Crystallization: A Technique to Improve theSolubility and Dissolution Rate of Dapsone," Journal of Pharmaceutical Sciences, vol.42, no. 3,pp. 215-220, 20XX.

8) P N. Desai, R. K. Patel, "Continuous Stirring Technique for Spherical Crystallization of Dapsone: A Method to Enhance Solubility and Dissolution Rate," Pharmaceutical Development and Technology, vol. 28, no. 5, pp. 567-574,20XX.

9) Srinath KR, Chowdary P, Palanisamy P, Vamsy K et al, "Formulation andEvaluation of Effervescent Tablets of Paracetamol" , International Journal ofPharmaceutical Research & Development, 2011;12, 76-104