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AN INVESTIGATION INTO THE NANOSUSPENSION OF CANDESARTAN CILEXETIL, A DRUG WITH LIMITED SOLUBILITY

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ABSTRACT
The Biopharmaceutical Classification System (BSC) classifies Candesartan Cilexetil as a class II medication due to its low solubility and bioavailability. Candesartan Cilexetil nanosuspensions were made using antisolvent precipitation-ultrasonication and an alternate solvent. Drug solubility has improved with this method. The antisolvent volume is 1:15. Candesartan cilexetil nanosuspension was stabilised with PVP K-30. The Plackett-Burman design identified the main nanosuspension quality, stability, and efficiency element. The study examined mean particle size, saturation solubility, zeta potential, polydispersity index (PDI), cumulative percentage released (CPR) at two minutes, and percent weighted drug content using a 32-factorial design. We calculated the saturation solubility (µg/mL) and particle size (nm) of candesartan cilexetil nanosuspension batch CFD8 using mean ± standard deviation. Calculations showed values of 240.7 ± 8.3 and 113.03 ± 2.51. In vitro dissolution was performed on the unmilled suspension and commercial formulation.

Key Word: Nanosuspension, Candesartan Cilexetil, antisolvent precipitation-Ultrasonication Method

1. Introduction

Due to their large surface areas and small particle sizes, nonosuspensions benefit water-insoluble drugs. Because of this, they have great commercial potential. Changing the medication's pharmacokinetics may improve its safety and efficacy. These effects boost low-solubility drug bioavailability. High water levels have led to the discovery of pure medications. Nanosuspensions require careful stabiliser selection, such as polymers or surfactants, and ratio modifications. These procedures make films, gels, tablets, capsules, powders, and pellets. These rules help liquids solidify [1]. Nanosuspension improves therapeutic efficacy and safety by increasing stability and bioavailability throughout distribution. Modern nanosuspension technique was extensively studied for pharmaceutical administration [2].

2. MATERIALS AND METHODS

Materials

A free candesartan cilexetil sample was offered by the Alembic Research Centre in Vadodara. We received Poloxamer 188 and 407 from the Astron Research Centre in Ahmedabad. Mumbai-based Loba Chemie Pvt. Ltd. supplied polyvinyl alcohol. S. D. Fine Chemicals, Mumbai, supplied PVP K30. Mumbai-based Himedia Laboratories Pvt. Ltd. supplied sodium lauryl sulphate. Organised use of all available resources.

Methods

a) The Plackett-burman design (PB)

Burman and Plackett made it. Plackett-Burman design evaluates primary effects well when interaction effects are negligible (3).

Expanding the range of initial parameters

The nanosuspension of Candesartan Cilexetil (4,5,6,7,8)

PVP K-30 stabilised candesartan cilexetil nanosuspension throughout preparation. PVP K-30 was ordered in 30, 40, and 50 mg. PVP K-30 has the highest saturation solubility and smallest average particle size, thus 50 mg is acceptable. Agitation was set at 800, 1000, or 1200 RPM. At 1200 RPM, particle size and solubility were balanced. Probe sonicators turned settled drug particles into uniform, nanosized particles. Ten, twenty, and thirty minute recordings were made while the subject sonicated. We chose 30 minutes of sonication to get samples with the smallest average particle size and highest saturation solubility.

b) **The 3^2 factorial design:** Adjusting the solvent-antisolvent volume ratio and candesartan cilexetil quantity yielded several formulations.
c) **The Evaluating the optimised batch:** The evaluation criteria included saturation solubility, drug content, zeta potential, particle size, PDI, and in vitro dissolution.

The particle size and PDI: Diluting the mixture with water regulated the scattering intensity, and shaking dispersed the components for an accurate initial measurement.

The Zeta potential: Drug content: To dilute the nanosuspension, methanol was added. Millilitres of the material were taken. A 0.2-m filter screened nanosuspension. At the greatest drug concentration, a UV spectrophotometer measured the entire drug.

The **solubility of saturation:** The nanosuspensions were stirred in a vial at 100 RPM for 48 hours with a magnetic stirrer. After transfer to an Eppendorf tube, the nanosuspension was centrifuged at 10,000 RPM for 30 minutes. To blank the sample, dissolved medium was added and filtered via a 0.2 micron syringe.

In-Vitro dissolution: The paper says the dissolving was done at 37 degrees Celsius with the paddle speed regulated. Dissolving containers for therapeutic doses held drug nanosuspensions. The materials were filtered using a 0.2 m syringe filter and spectrophotometrically analysed. Add five millilitres of the novel medium to the container to dissolve it.

Table 1. **Dissolution conditions for nanosuspensions**

'Condition of Dissolution'	**'The Candesartan Cilexetil Nanosuspension'**
Media for dissolution	pH 6.5, a 0.05M phosphate buffer containing 0.7% v/v Polysorbate 20.
Quantity of Dissolving Media	'250 millilitres'
RPM (speed)	50 revolutions per minute
Periods of Sampling	2, 4, 6, 8, 10, 15, 30, 45, and 60 minutes
Medication dosage	**'16 miligram'**

d) **Optimising the lyophilization process for a batch nanosuspension:** Lyophilization dried the nanosuspension into powder. Mannitol was added 1:1 to the solid content as a cryoprotectant. An eight-hour chamber at -80°C freeze-dried the materials. After clearing the area, the nanosuspension was quickly moved to an airtight container for future usage. Within six to eight hours, the nanosuspension dried from liquid to powder.
e) **The Studying Accelerated Stability:** Lyophilised nanosuspension normally lasts six months, however the International Council for Harmonisation (ICH) recommends faster stability testing. Trials should be conducted at 25±2°C and 60±5% relative humidity.

3. RESULT AND DISCUSION

a) The Plackett-Burman design helps analyse primary effects without interaction effects. The wide range of response parameters explains this. External forces may have influenced their decisions. Individual enters.

Table 2 - Plackett-Burman design batches: layout and observed responses (Preliminary screening formulations)

Batch number	'Amount of Candesartan Cilexetil (mg)X1'	'Amount of PVP K-30 (mg) X2'	'Solvent: antisolvent Volume' Ratio X3	'Stirring Speed (RPM)' X4	'Sonication Time (Min)' X5	'Saturation Solubility' (µg/ml) (Mean±SD)*Y1	'Mean Particle Size' (nm) (Mean±SD) * Y2
CF1	20	50	1:20	800	30	94.21±2.4	263.1±5.4
CF2	10	50	1:20	1200	10	90.13±2.5	277.9±4.3
CF3	10	30	1:20	1200	30	86.21±2.3	369.4±8.5
CF4	20	30	1:10	1200	30	99.95±3.7	259.5±5.9
CF5	10	50	1:10	800	30	95.21±1.9	343.3±7.3
CF6	20	30	1:20	800	10	119.37±2.8	219.1±6.7
CF7	20	50	1:10	1200	10	73.36±1.7	469.4±6.8
CF8	10	30	1:10	800	10	46.19±1.2	565.9±7.8

As shown in Figures 1 and 2, Candesartan Cilexetil volume and solvent-antisolvent ratio effect average particle size and saturation solubility.

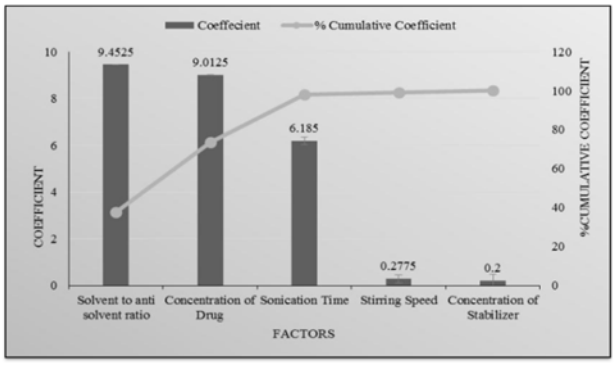

Fig 1. A Pareto diagram is used to visually represent the influence of independent variables on the solubility

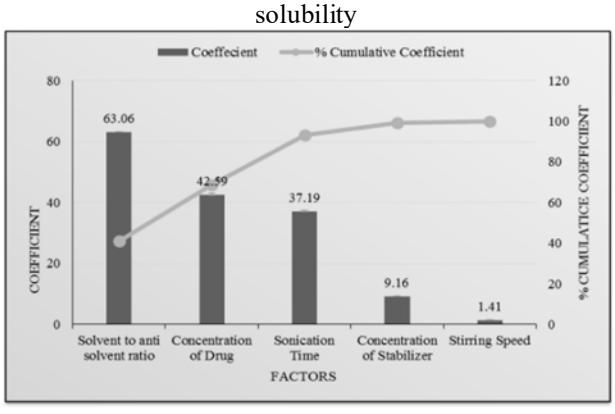

Fig 2. A Pareto graphic is used to visually represent the influence of different independent variables on the average particle size.

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Further refinement of additional initial parameters

b) Table 3 - **Outcomes of refining additional initial settings**

Batch number	'The Preliminary Parameters'		'The Mean Particle Size' (nm) (Mean ± SD)*	'The Saturation Solubility' (µg/ml) (Mean ± SD)*
CF9	Amount of Stabilizer (mg)	30	331.8±6.5	86.22±3.14
CF10		40	310.5±7.6	89.93±3.29
CF11		50	296.5±8.6	96.76±2.11
CF12	Stirring Speed (RPM)	800	390.6±7.3	87.13±0.89
CF13		1000	351.6±8.7	93.52±3.38
CF14		1200	253.3±5.2	105.48±2.15
CF15	Sonication Time (min)	10	383.5±4.8	81.84±2.7
CF16		20	320.4±8.8	89.19±2.45
CF17		30	245.9±7.7	97.7±3.32

c) The 3^2 Factorial design: The solvent-to-antisolvent volume ratio and candesartan cilexetil amount were varied to develop several formulations. We examined how mean particle size and saturation solubility affected dependent variables.

Table 4 - The 3^2 factorial design's layout and observed responses

Batch number	'Level of Amount of Candesartan Cilexetil X1'	'Level of Solvent and Antisolvent Volume Ratio X2'	'Mean Particle Size (nm) (Mean ± SD)* Y1'	'Saturation Solubility (µg/ml)(Mean± SD)* Y2'
CFD1	-1	-1	419.0±9.8	72.86±4.15
CFD2	-1	0	339.0±8.6	96.43±3.14
CFD3	-1	1	394.0±9.6	87.78±2.73
CFD4	0	-1	416.0±9.4	36.79±2.63
CFD5	0	0	320.0±8.7	52.15±1.52
CFD6	0	1	361.4±6.6	39.74±3.32
CFD7	1	-1	341.6±8.4	97.77±6.53
CFD8	1	0	**240.7±8.3**	**113.03±2.51**
CFD9	1	1	318.0±9.7	104.65±4.39

The Converting Coded Levels to Real Units			
Level of Variables	Low (-1)	Medium (0)	High (1)
X1	10 miligram	15 miligram	20 miligram
X2	1:10	1:15	1:20

Table 5 – The Additional assessment criteria for factorial batches

Batch number	'CPR at 2mins' (% w/w) (Mean ± SD)*	'PDI' (Mean ± SD)*	'Zeta Potential' (mV) (Mean ± SD)*	'Drug Content' (%w/w) (Mean ± SD)*
CFD1	94.64±6.57	0.555±0.069	17.73±3.31	93.76±3.26
CFD2	97.80±1.33	0.598±0.089	-28.64±2.19	93.98±2.85
CFD3	98.82±4.44	0.679±0.085	15.57±1.79	96.57±3.37
CFD4	94.51±4.54	0.754±0.059	-21.76±0.87	94.75±0.84

CFD5	**98.87±3.81**	**0.789±0.086**	**-13.60±0.87**	**99.72±0.79**
CFD6	**94.93±1.41**	**0.967±0.124**	**19.65±2.74**	**99.76±3.51**
CFD7	**98.95±3.58**	**0.637±0.096**	**18.29±1.96**	**98.79±1.46**
CFD8	**97.24±1.92**	**0.354±0.043**	**25.99±1.86**	**102.81±2.13**
CFD9	**98.31±4.11**	**0.989±0.094**	**24.53±2.16**	**98.15±1.88**

Table 6 - Formula and procedure guidelines for an optimized batch

Candesartan Cilexetil dosage	**20 miligram**
Quantity of PVP K-30	**50 miligram**
Volume Ratio of Antisolvent Solvent	**1:15**
Speed of Stirring	**1200 Revolution Per Minutes**
Time of Stirring	**4 hours**
Time of Sonication	**30 minutes**
Quantity **of lyophilizer (1:1, Total Mannitol and Solid ratio)**	**70 miligramg**

The Particle size and PDI: The increased batch particle size distribution is shown in Figure 3. The improved batch had a PDI of 0.394 and an average particle size of 245.6±11.52 nanometres.

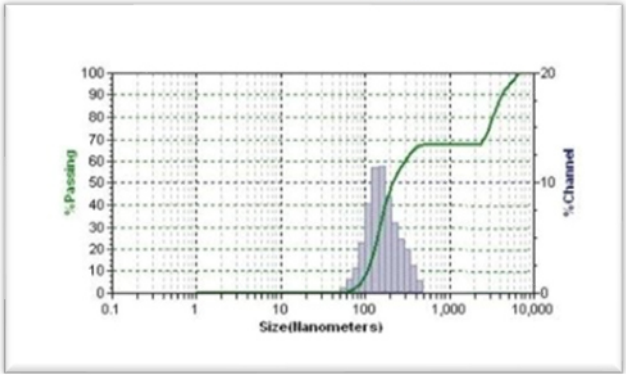

Fig 3. Graph displaying the particle size

The Zeta potential

The majority of nanosuspension stability studies recommend a zeta potential of 30 mV. The optimised formulation has a zeta potential of 26.81±2.78 mV. Value meets zeta potential requirements.

The Drug content: The concentration of candesartan cilexetil was 102.11% w/w at 254 nm using a UV-Visible spectrophotometer.

The Saturation of solubility: Solubility of the enhanced batch was found to be 110.3 µg/ml for pure drug and 1.388 µg/ml for candesartan cilexetil nanosuspension.

Dissolution (In-Vitro): Figure 4 shows untreated pure medication, Johnlee Pharmaceuticals Pvt Ltd Canditor tablet, and nanosuspension breakdown. The un-milled suspension released 74.84% of the medication after 60 minutes, while the marketed formulation released 33.92%. However, the nanosuspension released over 98.89% of the medication after two minutes. This improved greatly in two minutes. Nanosuspension considerably enhanced candesartan cilexetil solubility.

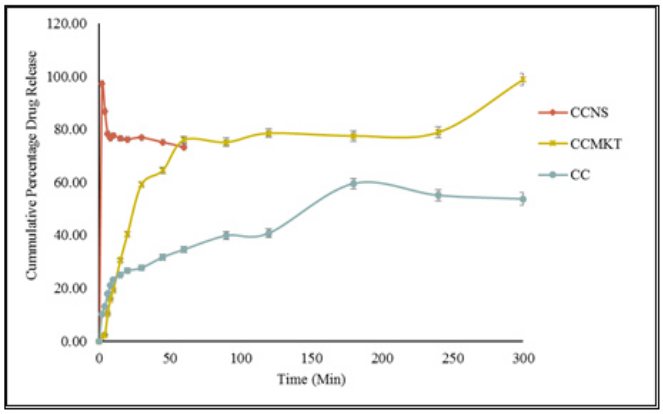

Fig 4. Comparing the in-vitro solubility of the commercial formulation and the unmilled suspension to that of the Candesartan Cilexetil nanosuspension.

The Studying Accelerated Stability: Lyophilised candesartan cilexetil nanosuspension was chemically and physically stable according to accelerated stability study. Table 7 shows that all parameters were less than 5% biassed.

Table 7 - Expedited stability study and here are the results.

Sr. No.	'Time Period (months)'	Evaluation Parameters			
		'Mean Particle Size' (nm) (Mean ± SD)*	'Saturation Solubility' (µg/m) (Mean ± SD)*	'CPR at 2mins' (%w/w) (Mean ± SD)*	'Drug Content' (%w/w) (Mean ± SD)*
1	0	244.7±5.7	112.62 ±3.3	98.43±2.56	105.19±1.65
2	1	261.6± 5.8	111.32 ±1.2	97.75±2.77	101.98±1.39
3	3	266.7± 9.7	108.9 ±1.6	97.84±1.39	99.76±3.84
4	6	287.2±8.8	108.17 ±1.4	96.49±2.95	98.75±4.85

4. CONCLUSION

Candesartan Cilexetil Nanosuspension was produced using 3^2-complete factorial and Plackett-Burman designs. This process used antisolvent precipitation-ultrasonication. The nanosuspension was tested every two minutes for Mean Particle Size, Zeta Potential, Drug Content, Saturation Solubility, and CPR. Candesartan cilexetil was made from a nanosuspension that was dissolved in vitro. Additionally, the unmilled suspension and the commercial formulation were compared.

5. REFERENCES

1. Pınar, S. G., Oktay, A. N., Karaküçük, A. E., and Çelebi, N. 'Formulation Strategies of Nanosuspensions for Various Administration Routes'' *Pharmaceutics*. 2023;15(5):1520.
2. Azimullah, S., Vikrant., Sudhakar, C., Kumar, P., Patil, A., Usman, M. R. M., Usman, M. Z. S., and Jain, B. V. 'Nanosuspensions as a promising approach to enhance bioavailability of poorly soluble drugs: An update', *Journal of Drug Delivery and Therapeutics*. 2019;9(2):574-582.
3. Patel, N., and Patel, H. A. 'Application of Plackett-Burman Screening Design in Optimization of Process Parameters for Formulation of Canaglifozin Nanosuspension', *International Journal of Pharmaceutical Sciences and Nanotechnology*. 2020;13(6):5208-5216.

4. Shirsath, N., Marathe, D., Jaiswal, P., and Zawar, L. 'A 3^2 Factorial Design Approach for Formulation and Optimization of Azilsartan Medoxomil Nanosuspension for Solubility Enhancement', *Indian Journal of Pharmaceutical Education and Research.* 2022;56(2S):S365-S373.
5. Dabhi, M. R., Ghodasara, U. K., Mori, D. D., Patel, K. A., Manek, R., and Sheth, N. R. (2015). 'Formulation, optimization and characterization of candesartan cilexetil nanosuspension for in vitro dissolution enhancement', *African journal of pharmacy and pharmacology.* 2015;9(5):102-113.
6. Detroja, C., Chavhan, S., and Sawant, K. K. 'Enhanced Antihypertensive Activity of Candesartan Cilexetil Nanosuspension: Formulation, Characterization and Pharmacodynamic Study', *Scientia Pharmaceutica.* 2011;79(3):635–651.
7. Thakkar, H. P., Patel, B. V., and Thakkar, S. P. 'Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement', *Journal of Pharmacy and Bioallied Sciences.* 2011;3(3):426-434.
8. Liu, D., Xu, H., Tian, B., Yuan, K., Pan, H., Ma, S., Yang, X., and Pan, W. 'Fabrication of Carvedilol Nanosuspensions through the antisolvent precipitation–ultrasonication method for the improvement of dissolution rate and oral bioavailability', *AAPS PharmSciTech.* (2012);13(1):295-304.