International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 964-973 www.ijprajournal.com ISSN: 2249-7781

Solubility Enhancement of Azelnidipine by Using Microwave Assisted Nanocomposites

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Submitted: 12-01-2023 Accepted: 24-01-2023

ABSTRACT
Dissolution and diffusion through the gastrointestinal membrane are the mechanisms by which drugs get absorbed on oral administration. The major challenge in the case of most of the drugs is poor water solubility. Hence the main aim of the present study is to develop Nanocomposites by microwave-assisted technique to enhance solubility and dissolution of poorly water-soluble drug Azelnidipine.Synthetic polymers such as Soluplus were selected for Nan composites preparation based on its wetting and surface active agent property. Nanocomposites were prepared by Microwave-assisted technique.The solubility and dissolution enhancing the performance of Nan composites were assessed by In-vitro solubility and dissolution studies.

KEYWORDS: Dissolution Study, Nanotechnology, BCS classII drug, Microwave assisted technique

I. INTRODUCTION

The oral route of drug administration is the route of choice for the formulators and continues to dominate the area of drug delivery technologies. However, though popular, this route is not free from limitations of absorption and bioavailability in the milieu of gastrointestinal tract. Whenever a dosage form is administered orally, drug in the dosage form is released and dissolves in the surrounding gastrointestinal fluid to form a solution. This process is solubility limited. Once the drug is in the solution form, it passes across the membranes of the cells lining the gastro-Intestinal tract. This process is permeability limited. Then onwards the drug is absorbed into systemic circulation. In short, the oral absorption and hence bioavailability of drug is determined by the extent of drug solubility and permeability.

DISSOLUTION

Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.

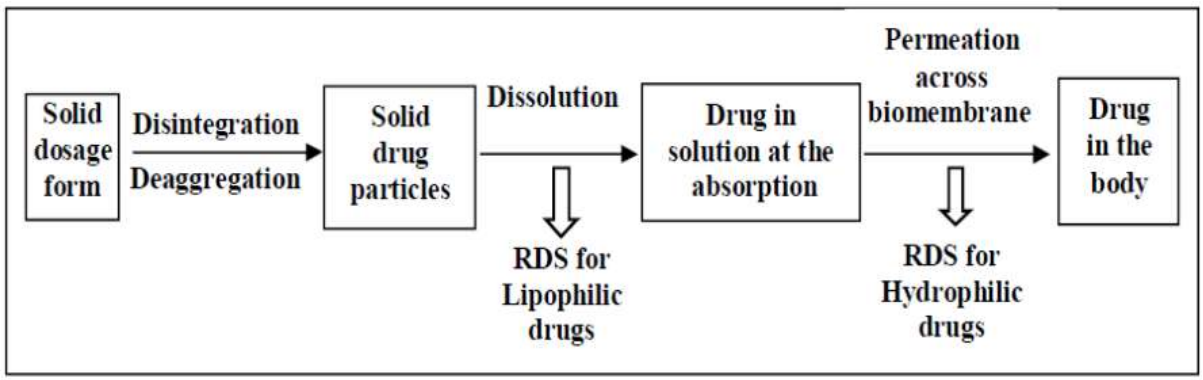

Figure 1: Two rate determining steps (RDS) in the absorption of drugs from orally administered formulations

Dissolution is a kinetic process and the rate of dissolution reflects the amount of drug dissolved over a given time period. The rate at which a solid dissolves in a solvent was proposed by Noyes and Whitney in 1897 and elaborated subsequently by other workers. The equation can be written as:

$$\frac{dM}{dt} = \frac{DS}{\mathbf{h}}(C_s - C) \text{ OR } \frac{dC}{dt} = \frac{DS}{\mathbf{Vh}}(C_s - C)$$

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CHARACTERIZATION OF POLYMER:

a. **Swelling index**:

1 gm. soluplus in accurate weight and then transferred to 100ml measuring cylinder. After this, the occupied initial volume by was noted down for calculations. Using distilled water, the volume was then adjusted. The cylinder (open end) is sealed with aluminum foil and kept aside for 24 Hours. After 24 hrs. of storage the volume of swelled gum were noted. Using the formula given below, the swelling index of every polymer was calculated.

$$\%\ \text{swellingindex} = Xt - Xo \times 100$$

Where, SI- Swelling index of gum, Hi - Initial height of powder, Hf- Final height of powder after 24 hr.

b. **Foaming index**:The foaming index calculated to check the surfactant properties of the gum. 1 gm of soluplus was weighed accurately and then shifted to 250 ml measuring cylinder. The 100ml of distilled water was incorporated in measuring cylinder to make dispersion. The resultant dispersion was shaken vigorously for 2mins. The foaming index of each polymer calculated by the following equation

$$\text{Foaming index} = Hf - Hi$$

Where, Hf = Height of solution of gum after shaking;
Hi = Height of solution of gum before shaking.

c. **Viscosity Determination**:

The viscosity were calculated by dissolving one gram of each polymer in 100 ml of water (1% w/v solution).The carrier dispersions viscosity of each polymer were measured by Brookfield viscometer using spindle 63 at 100 rpm.

PREPARATION OF NANOCOMPOSITES

For each sample, a physical mixture of Azelnidipine and the pregelatinized starch was made by homogenous mixing. The weight to weight (w/w) ratio of the drug and carriertaken from 1 to 6 ratios keep constant add 5 ml water each gram made homogeneous slurry. A fixed amount of slurry was placed in a glass beaker with a Teflon stirrer (transparent to microwave) and treated with microwave irradiation for different times at power of 400W (Electrolux MC009SS). The temperature of the mixture at the end of treatment was recorded. The sample was then ground in the mortar and pestle and sieved to achieve a particle size of 80-250µm. The Nanocomposites of drug with the carrier respectively. The process variable is shown in the below.

Table 1:process variable for preparation of Azelnidipine Nanocomposites

Sample	Ratio (w/w)	Time (min)	Final temp. range (^{0}C)
Azelnidipine + Soluplus	1:1	24	180
Azelnidipine +Soluplus	1:2	24	200
Azelnidipine +Soluplus	1:3	24	220
Azelnidipine +Soluplus	1:4	24	180
Azelnidipine +Soluplus	1:5	24	240
Azelnidipine +soluplus	1:6	24	200

EVALUATION OF NANO COMPOSITES:

Solubility studies:

The solubility of Azelnidipine and Solubility of Azelnidipne with soluplus polymer is determined in water. The solubility of drug and Nanocomposites was determined by taking an excessive amount of drug (40 mg), Nano composites (equivalent to 40 mg drug) and added them in 10 ml of above solvent, in vials. The samples were kept at equilibrium for a period of 72 hrs, in an incubator at 37±0.500C with occasional shaking. The supernatant collected from vials was filtered through Whatman filter paper and analyzed by UV- visible spectrophotometer (Shimadzu 1800) at the respective wavelength.

Drug Content Analysis:

Drug content analysis was performed to study the amount of drug incorporated in the nanocomposites. Azelnidipine was extracted from the Nanocomposites by dissolving then in 25 ml methanol. The resulting solution was filtered through a 0.45 microns membrane filter. The Azelnidipine content in the Methanolic extract was analyzed spectroscopically by using UV-Visible

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spectrophotometer at a wavelength 268nm, against Methanol as a blank.

% **Drug Content = $W_a/W_t \times 100$**
Where,
W_a= Actual drug content,
Wt = Theoretical drug content \

DISSOLUTION STUDY OF AZELNIDIPINE NANOCOMPOSITES:

The dissolution test of an optimized ratio was carried out following the USP XXIV Apparatus 2 (paddle) method. The dissolution media, paddle speed, bath temperature, and UV analysis done as per Table 2. 5 ml Of Aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after Filtration through Whatman filter paper (No.41), were analyzed spectroscopically.

Table 2: Dissolution Studies of Azelnidipine Nanocomposites

Drug : Polymer	Dissolution Medium (900)ml	Paddle speed (RPM)	Total Time (hr)	Sample interval (min)	Bath Temperature	UV analysis (wavelength nm)
1:1	HCL+NACL	50	2	5,10,15,20,25,30	37 +0.5C	268

FORMULATION &PREPARATIONS OF MOUTH DISSOLVING TABLET

The ratios of Nan composites that showed the best result in the solubility and dissolution studies were selected for mouth dissolving Tablet formulation of microcrystalline cellulose use as diluent and sodium starch use as disintegrant. All the component of the tablet sieved through a ≠ 60 sieve weight mixed compressed by direct compression.

Table3.Content of Mouth Dissolving Tablet of Azelnidipine Nanocomposite

Ingredients	F1	F2	F3	F4	F5	F6
AZS (pm)	8	8	8	8	8	8
Microcrystaline cellulose	50	52	54	56	58	60
Sodium starch glycolate	8	8	10	10	12	12
Mannitol	130	128	126	124	122	120
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2

EVALUTION OF MOUTH DISSOLVING TABLET

PRE-COMPRESSION STUDY:

The pre-compression evaluation included measurement of the angle of repose, Carr's index (compressibility) and Hausner's ratio of optimized Nanocomposites and various formulation mixtures, following the procedures given in USP 30 (2007).

POST-COMPRESSION STUDY:

Post-compression evaluation included measurement of weight variation, hardness, friability, drug content and disintegration time of prepared formulations, following the procedures given in USP 30 (2007).

IN-VITRO STUDIES:

An In-vitro drug release studies of the prepared nine formulations of Mouth dissolving tablets were conducted for 40 min using eight stations USP Type 2 Apparatus (paddle type). The agitation speed was 50 rpm. Azelnidipine tablet was added to 900 ml HCL+NACL at 37 ± 0.50C. 5 ml aliquots were withdrawn at time intervals of 5, 10, 15, 20, 25, 30 min. and filtered through Whatmanfilter paper no. 41. An equal volume of fresh dissolution medium was replaced to maintain the volume of the dissolution medium. The filtered samples were analyzed spectrophotometrically at 268 nm. The cumulative percentage of the labeled amount of drug released was calculated.

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STABILITY STUDIES:

Stability studies is an integral part of drug development program are one of the most important area's in the registration of pharmaceutical product. The purpose of Stability testing is to provide evidence on how the quality of drug substances or drug products varies with time under the influences a variety of environmental factor such as temperature, humidity, light, and enables recommended conditions, re-test periods and shelf half-life to be established. The products was analyzed an intervals for various parameter which may include dissolution time, disintegration time, appearance, stability has been conducted at following conditions.

Accelerated stability study was carried out as per ICH guidelines. The optimized sample of Nan composites was placed at 40+2C for 3 month in stability chamber and 75+5%RH. Various parameters such as drug content, appearance and in-vitro drug released were measured after 1,2 and 3 month of stability study. Result of stability study are shown in Table no-12

II. RESULT AND DISCUSSION

EVALUATION OF NANOCOMPOSITES:

SOLUBILTY STUDIES:

Solubility studies were performed to analyze the solubility enhancing properties of Nanocomposites. Solubility studies provided the basis for selection of the best ratios that was to be forwarded for formulation. This aspect was investigated by performing scanning electron microscopy.

Table 4: Solubility study of Azelnidipine in different Solvent

Sr.No	Media	Solubility
1	Distilled water	Insoluble
2	First fluid	54.29
3	Methanol	36.07

DRUG CONTENT DETERMINATION:

The various batches of the Nanocomposite were subjected for drug content analysis. The solid Nanocomposite (10mg) were dissolved in adequate quantity (10ml) of methanol. The UV absorbance was measured using a UV spectrophotometer at 253nm. Drug Content was found in the range 98.23% maximum drug content was observed for (F4) batch.

Table 5: Drug content of different batches of Nan composites

Sr. No.	Batch	Drug content
1	F1	91.74%
2	F2	86.75%
3	F3	95.67%
4	F4	98.23%
5	F5	96.31%
6	F6	96.54%

DISSOLUTION STUDIES:

Dissolution studies were performed to analyze the solubility enhancing properties of polymers. Dissolution studies gave the basis for the selection of best ratio that is to be forwarded for formulation. Nanocomposites of dr68ug with the polymer in the various ratios were analyzed for solubility determination. The results of the same are shown in Table 5. These studies reveal that soluplus having very good solubility enhancing property as they have good surfactant properties and reduction of crystal size of the drug to nanoscale in the form of Nanocomposites enhances the solubility. Solubility studied of Nanocomposites indicated that as the ratio of drug to polymer increases solubility also increases. It was also found that after a certain ratio i.e. 1:6 solubility remainsconstant hence 1:6ratio was optimized Batch.

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Table 6: Dissolution study of Nanocomposites

Time	AZ	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
5	9.29	10.51	13.10	15.50	16.20	17.10	17.30
10	14.23	13.50	15.60	17.83	17.39	17.84	18.14
15	15.47	20.12	18.81	20.86	21.40	21.66	22.44
30	20.73	21.40	25.17	34.67	38.10	38.13	41.15
45	25.57	34.34	39.76	46.10	47.59	48.1	48.12
60	32.70	47.52	50.45	51.03	53.13	53.13	53.72
90	39.08	55.13	61.17	62.28	63.32	59.60	60.18
120	44.00	55.18	63.45	64.46	68.44	64.58	66.17

CHARACTERIZATION OF NANOCOMPOSITES
FOUIR-TRANSFORM INFARED RAY SPECTROSCOPY

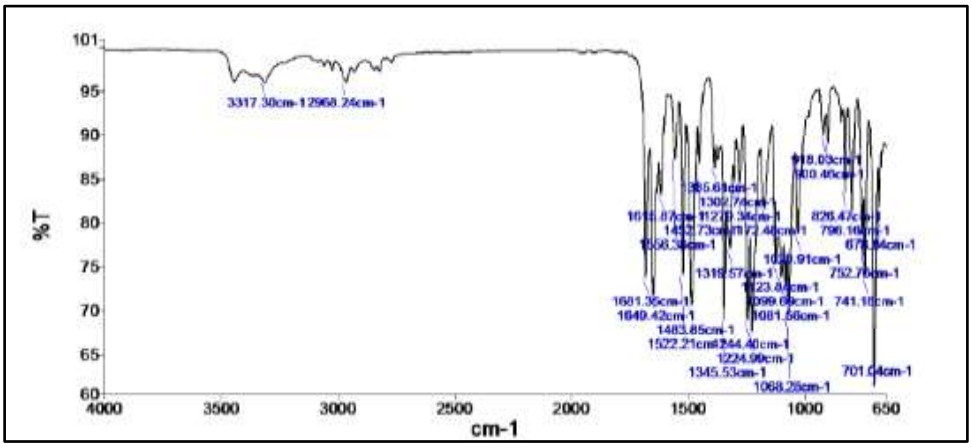

Figure 2: FT-IR of Azelnidipne

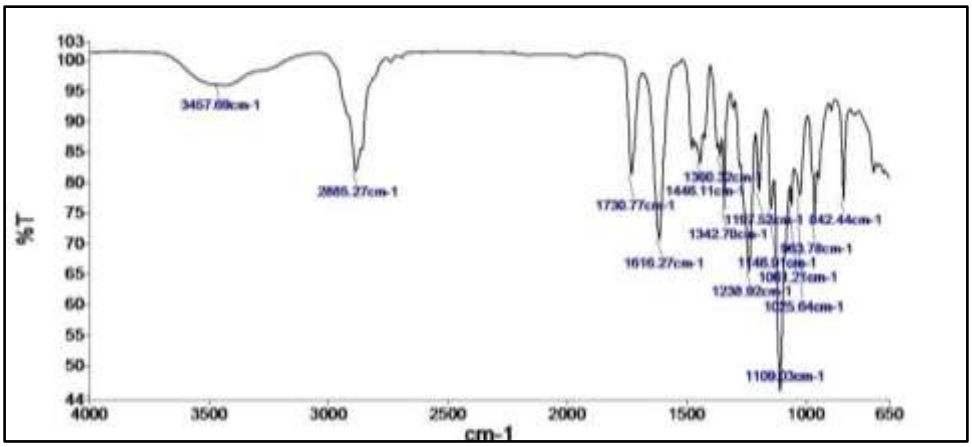

Figure3: FT-IR ofSoluplus

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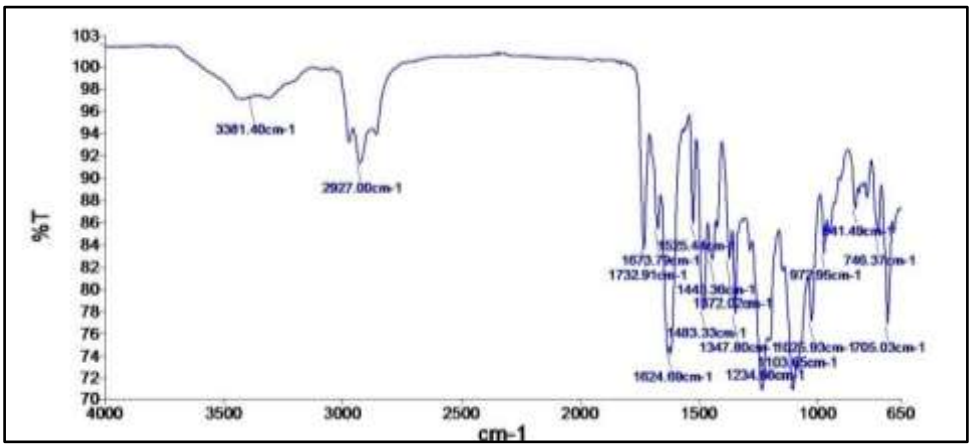

Figure 4: FT-IR of Azelnidipne with physical mixture

Table 7: FTIR Ranges of Azelnidipne (physical mixture) with soluplus

Sr.No.	Functional Group (cm^1)	AZELNIDIPINE (physical mixture)
1	Aromatic 1^0 amine (N-H stretch)	3500-3300
2	C-N (Aromatic 3^0 amine, CN stretch	1360-1310
3	Aromatic 2^0 amine (N-H stretch)	~3450
4	C-N (Aromatic 2^0 amine, CN stretch	1370-1280
5	-N-O	1355-1320
6	Ester	1750-1725

EVALUATION OF MOUTH DISSOLVING TABLETS

PRE-COMPRESSION EVALUATION

All the formulation mixtures were subjected to measurement of the angle of repose, Carr's index and Hausner's ratio. The results are shown in Table no.8. From the angle of repose, Carr's index and Hausner's ratio data, it can be clearly concluded that Azelnidipine and its mixture with different formulation components have excellent flow properties and fair to- good compressibility.

EVALUATION OF MOUTH DISSOLVING TABLET

PRECOMPRESSIONAL STUDY

All the formulationmixture was subjected to measurement of angle of repose, Carr's index and Hausner's ratio, the result are shown in Table from above these values it is concluded that Azelnidipine and its mixture with different formulation components have excellent flow properties and fair to good compressibility, these mixture is directly subjected to the direct compression into tablets and mixture having good flow from the hopper with good content uniformity in the final tablets.

Table 8:Pre-compression of powder Blends

Formulation code	Bulk density (mg/ml)	Tapped density (mg/ml)	Hausners ratio	Compressibility index (%)	Angle of Repose
F1	0.44±0.001	0.58±0.007	1.11	12.07	24.34
F2	0.42±0.004	0.55±0.004	1.13	14.19	25.67
F3	0.46±0.003	0.57±0.005	1.16	15.06	30.72
F4	0.46±0.007	0.58±0.007	1.14	16.31	27.93
F5	0.44±0.002	0.52±0.007	1.20	14.34	29.02
F6	0.45±0.002	0.57±0.006	1.15	15.34	30.1

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POST COMPRESSION EVALUATION

Prepared formulation was subjected to post comments post-compression evaluation such as Hardness, Friability disintegration time of prepared tablets, or weight variation. The result are shown Table no 9.

Table 9: Evaluation of Tablets characteristic

Batch No	Thickness (mm)	Hardness (kg/cm²)	Friability %	Weight variation (mg)	Disintegration Time (Sec)
F1	3.42 ± 0.03	4.1 ± 0.78	98.5±89	198.75±0.32	38.21±0.08
F2	3.56 ± 0.03	4.5± 0.02	96.7 ± 23	199.2±19	35.18±0.12
F3	4.41 ± 0.03	4.1 ± 0.02	98.7±40	196.3±98	34.52±0.07
F4	4.52 ± 0.02	4.5 ± 0.06	99 ± 46	199.3± 98	22.36±0.05
F5	4.32±0.074	4.3±0.04	97 ± 45	199±67	27.58±0.010
F6	4.32± 0.074	4.3 ± 0.74	99 .8± 23	198.7 ± 09	28.45±0.09

Table 10: Evaluation of wetting time & wetting absorption

Batch	Wetting time(sec)	Water absorption ratio (sec)
F1	35.07±0.02	39.24±1.01
F2	30.52±0.05	30.52±0.05
F3	28.36±0.12	28.36±0.2
F4	17.79±0.13	73.38±1.15
F5	21.32±0.09	68.19±1.07
F6	23.91±0.17	61.27±0.97

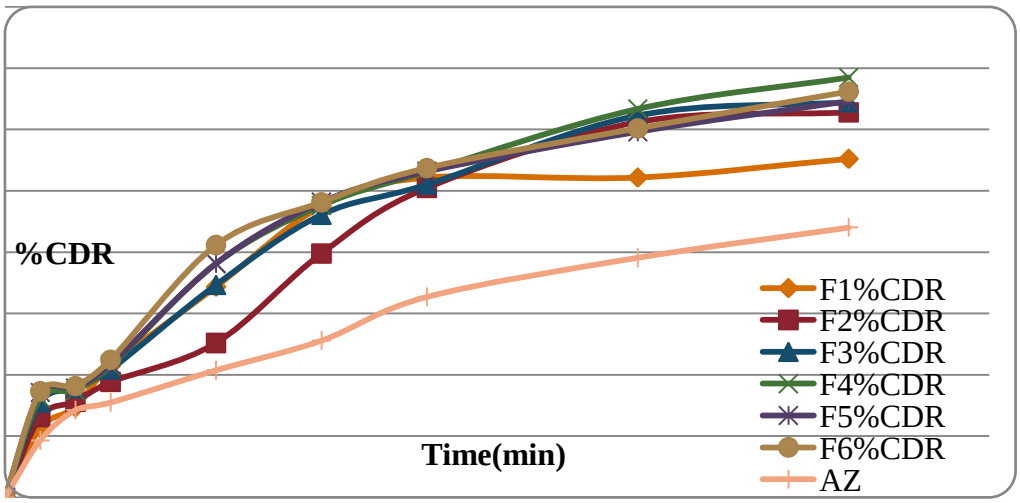

Figure 5: in vitro drug release study of azelnidipine

IN-VITRO DRUG RELEASE: The optimized formulation (F4) is depend on disintegration studies, were subjected to an in-vitro drug release study. The formulation (F4) shows more drug release as compare to other batches.

DRUG DISSOLUTION KINETIC:

Various kinetic parameters studied for Azelnidipine Nanocomposites formulation are illustrated in Table 9. The Nano composite formation process led to greater drug dissolution rates compared with the rate for the drug alone;

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around 50% of the loaded drug dissolved within the first 5 min for Azelnidipine Nano composites. From the R2 value, it was concluded that the drug release profile of azelnidipine (Nanocomposites) Mouth Dissolving tablet followed the First order release pattern.

Table 11: Expected parameter and drug-release kinetic Models

Kinetics models	Parameter	Formulation Tablet
Zero Order	R^2	0.963
First order	R^2	0.988
Higuchi	R^2	0.919
Korsmeyer -peppas	R^2	0.836

STABILITY STUDY:

The optimized formulation was subjected to stability studies according to ICH guidelines. Various variables, such as drug content, disintegration time and in-vitro drug release, were measured before and after 30, 60 and 90 days of storage. The results of stability studies are shown in Table 10. There was no significant change in the variables mentioned above following the elevated temperature and humidity conditions imposed during the stability study. Thus, it can be concluded that the prepared formulation is stable and not much affected by elevated humidity and temperature.

Table 12: Stability data of optimized formulation

Duration (Months)	Appearance	Drug content(%)	InVitro released
0	Yellow granules powder	98.23±0.54	83.16±0.23
1	No change	97.56±0.56	81.10±0.45
2	No change	98.56±0.34	82.23±0.43
3	No change	98.02±0.45	83.10±0.56

III. CONCLUSION:

From all observations and results obtained it can be concluded that;

All the prepared formulations show satisfied Organoleptic properties.

The Preformulation study suggests that;

- The Drug and polymers used were of required quality and standards.
- The important feature of the study is uniform distribution of stable and easily produced drug formulation in the Nano-crystalline form in optimized Nano composites
- It is likely achievable to improve the solubility of poorly-soluble BCS class II drugs with the help of cheap natural as well as synthetic polymers using MIND technique.

As a final note, from the results, it can be concluded that microwave generated NCs can successfully be utilized to enhance solubility, dissolution and eventually the bioavailability of poorly soluble BCS class II drugs.

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