



Microwave Irradiation Technique, a Green Chemistry Approach for Dissolution Enhancement of Lopinavir

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: This research was focused on improvement of aqueous solubility of Lopinavir (LPO), Antiretroviral (ART) drug by preparing solid dispersion (SD) through microwave irradiation (MWI) technique as a green chemistry approach.

Place and Duration of Study: Department of Pharmaceutics, M. C. E. Society's Allana College of Pharmacy, CIF-SPPU, Pune, between June 2018 and July 2021

Methodology: In MWI different batches of SD were formulated by 3² factorial approach with time of exposure (X1) and power of radiation (X2) as variable quantity and dissolution rate as response (Y1). β -CD was used as hydrophilic carriers. Drug carrier magnitude relation of 1:1 resolve by phase solubility analysis and SD were assessed for drug content, percentage dissolution rate studies, FTIR, XRD, DSC and SEM analysis.

Results: The FTIR, XRD, DSC and SEM studies exhibited no interaction between LPO and excipient. In Physical mixture (PM) it shows less intensity and disappearance of sharp peaks while in SD indicates the conversion of crystalline state of LPO to amorphous state that discovered the dissolution enhancing, so the SD prepared by MWI proved to be a promising approach to increasing the dissolving rate of BCS class II drug LPO.

Conclusion: Hence, from the all analysis studies, it absolutely was evident that factorial batch F1 was the higher. F1 coded batch (LPO: β -CD within the magnitude relation of 1:1 with time of

exposure (4 min) and power of radiation (300 Watt), shows 07 folds increase i.e. 84% compared with drug discharged inside 60 min to plane LPO and SD i.e. 12 % only and 84% respectively.

Keywords: Lopinavir; microwave irradiation; solid dispersion; dissolution improvement.

1. INTRODUCTION

The answer of low liquid solubility for Active Pharmaceutical Ingredients (API) is that the most serious challenge within the formulation development of oral indefinite quantity types of poorly water-soluble medication. By the definition of the us formulary (USP), any compound having water solubility of <100 mg/ ml (0.1 mg / ml) is taken into account insoluble or much water insoluble, while, in line with the FDA steering for trade revealed in 2017, a compound is taken into account extremely soluble if the highest indefinite quantity strength is soluble in 250 ml or less of liquid media inside the pH scale vary of 01 to 6.8 at $37 \pm 1^\circ\text{C}$, and when a compound doesn't meet this demand, it's thought-about to possess low solubility [1]. According to varied estimates revealed within the literature, nearly 90 % of latest chemical entities and 75 % of compounds beneath development within the pharmaceutical trade make up the class of low liquid solubility and even 40 percent of top 200 oral drugs marketed in the USA have low solubility [2,3].

LPO, is chemically, [1S-[1R*(R*),3R*,4R*]]-N-[4-[[[2,6-Dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenyl methyl) pentyl] tetrahydro-a-(1-methylethyl)-2-oxo-1(2H)-pyrimidine cetamide [4]. LPO is a potent protease inhibitor used for the management of HIV infections which become a important component in combined chemotherapy commonly referred as Highly Active Anti-Retroviral Therapy (HAART), it shows poor bioavailability when administered orally [5-8]. LPO reveal low oral bioavailability due to its poor aqueous solubility 0.00192 mg/mL belongs to BCS Class II [9]. Generally the bioavailability of a BCS class II is rate restricted by its dissolution so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability [10]. Due to poor water solubility of protease inhibitor it show to be erratically and slowly absorption in GIT [11]. Various approaches , like amorphous SD [12-14] cyclodextrin complexation, [15] self-emulsifying drug delivery systems, [16] nanoparticle formation [17,18] etc., are applied to extend solubility and dissolution rates of compounds

with low water solubility. However, every of those methods has its own limitations and should not be applicable to any or all poorly soluble compounds.

MWI could be a well-known methodology for heating and drying materials. Microwave magnetic force irradiations are situated between the infrared and radio frequencies within the vary of 0.3–300 GHz, that corresponds to wavelengths of 01 mm to 01 m. Microwaves, is directly reworked into heat within the fabric due to their ability to penetrate into any substance, this is often because of moment of molecules that absorbs microwave energy and converts it into heat. Therefore, it's doable to accomplish fast and uniform heating even in materials exhibiting low heat physical phenomenon [19]. This mechanism is employed wide for drying, compound cross linkages, drug-polymer interaction and modification of the structure of drug crystallites through its effects of heating and/or electromagnetic field on the dosage forms. MWI offers many benefits such as: such as: rapid volumetric heating, no overheating at the surface, addressable heating, energy-saving and low operating cost. In addition the main advantage of not using organic solvents is the absence of any risk originating from residual solvents along with much shorter time [20]. The microwave heating is eco-friendly method or additionally referred to as green chemistry, this can be as a result of it doesn't produce any fuming gas or any risky by product along with risk of solvent entrapment along with API is also avoided [21].

The innovation in this research is that solvent free solid dispersion of LPO with beta cyclodextrin (β -CD) were successfully formulated by microwave irradiation. Design of Experiment (DoE) was used to understand the relationship between the Time of exposure of LPO to radiation and power of radiation were identified as variables.

2. MATERIALS AND METHODS

2.1 Materials

Analytical-quality chemicals were utilized as received. LPO was received as bequest trial from

Lupin Pharmaceuticals, Aurangabad. Polymers were purchased from Research lab, fine Chem Industries, Mumbai, India.

2.2 Methods

2.2.1 Compatibility studies

2.2.1.1 Fourier Transform Infrared Spectroscopy (FTIR) analysis

The FTIR studies of LPO, beta cyclodextrin (β -CD) and PM were carried out using (FTIR 4100 spectrophotometer, Jasco Corporation, Tokyo). LPO was subjected to Fourier transform infra-red spectroscopy studies to check the characteristic sharp peak of functional group. The potassium bromide (KBr) disk method was used for the preparation of sample. The sample of LPO was ground and mixed with potassium bromide in 1:9 ratio. The scanning range was 400-4000 nm^{-1} using potassium bromide as blank [22-24].

2.2.1.2 Phase solubility studies

The phase-solubility technique permits the analysis of the affinity between β -CD and LPO in ethanol. Phase-solubility studies were performed according to the method reported by Higuchi and Connors [25]. LPO, in amounts that exceeded its solubility, was taken in to 50ml beaker to which were added 30 ml of ethanol containing 1-10 mM of β -CD. The flasks were sealed with aluminum foil paper and shaken for 72 hrs at room temperature (28°C) on a magnetic stirrer. After equilibrating for 72 hrs aliquots of 5 ml were withdrawn and filtered immediately using 0.45 μm Whatman filter paper. The filtered samples were diluted suitably and assayed for LPO by measuring absorbance 260 nm against blanks.

The solubility experiments were conducted in triplicate. The apparent solubility constant (K_c) according the hypothesis of 1:1 stoichiometric ratio of complexes was calculated from the phase-solubility diagrams using equation 01 [26].

$$K_{a,b} = \text{Slope} / S_0(1-\text{slope}) \quad \text{Equation 01}$$

2.2.2 Preparation of solid dispersions

2.2.2.1 Microwave method

SDs of LPO with β -CD were prepared using microwave model-TDS (Samsung) by applying 3² full factorial experimental designs with the intention of investigating the joint influence of formulation, and process variables using Design Expert® (Version 12). In this study design, 2 factors are assessed, each at three tiers, and investigational trials were carried out in the nine possible combinations. The independent variables were the time of exposure (X1) and power of radiation (X2) as depicted in Table.1 and the % dissolution rate (Y1) was preferred as the dependent variable. SD of Drug and polymer were prepared by microwave induced fusion method. The finalized ratio was found to be 1:1 w/w for β -CD used. First the LPO and β -CD were weighed in a ratio of 1:1 followed by gentle mixing for 5 minutes using a mortar and pestle. The prepared sample were subjected to microwaves (Samsung-TDS microwave system, China) for different times and different power as described in factorial design as illustrated in Table 1. The samples were then collected and stored in desiccator for 48 hrs, and then the product was sieved through 18# sieve. The SD were and used for further studies [27].

Table 1. 3² Factorial Design for Microwave Solid Dispersion

Factorial Batches	Coded Form		Actual Form	
	X1	X2	X1(min)	X2(Power)
LPO: β -CD (1:1)				
F1	-1	-1	4	300
F2	-1	0	4	450
F3	-1	+1	4	600
F4	0	-1	6	300
F5	0	0	6	450
F6	0	+1	6	600
F7	+1	-1	8	300
F8	+1	0	8	450
F9	+1	+1	8	600

2.3 Evaluation of SD

2.3.1 Drug content analysis

The drugs-CD complex equivalent to 50 mg the LPO for SD of all batches of MWI technique were precisely weighed and transferred to a 10 ml graduated flasks. 5 ml ethanol was added individually and continuously shaken for 20 min, The solutions were sonicated for 5 minutes and the final volumes were made up to the mark with ethanol for both the drug. The solutions were filtered by Whatman filter paper 0.45 µm size. Then 1 ml sample solutions were withdrawn and diluted by 0.1 N HCl individually for preparing the desired concentration for spectrophotometric analysis at 260 nm of LPO. Every study was tried triplicate. The percentage of drugs content were calculated by the equation -02 [28].

$$\% \text{ Drug content(DC)} = M_{\text{act}} \div M_t \times 100$$

Equation 02

2.3.2 FTIR analysis

The FTIR studies of pure LPO along with SD prepared by MWI technique were carried out by using similar method describe earlier in compatibility study.

2.2.3 Optimization of the MWI SD batches of LPO with β-CD by Design-Expert (DoE) software

All the factorial batches of LPO SD by microwave technique were additionally optimized on the basis of evaluation parameter with the help of DoE (version 12). It is fascinating to develop a suitable pharmaceutical formulation while not wastage of staple in shortest potential time. It is thus terribly essential to know the quality of pharmaceutical formulation by using applied statistical tool such as factorial design. In addition to the art of formulation, the technique of factorial style is a good methodology of indicating the relative significance of variety of variables and their interaction. The range of experiment needed for these studies depends on number of freelance variables selected. A complete randomized factorial design of 3² was employed within the present study. The different independent variable included time of exposure and power for exposure applied. The batches were assessed for the result of individual variable was studied per response surface [29-32].

2.2.4 In vitro comparative drug release studies

The comparative drug release rate of Pure LPO, SD optimized batch of microwave SD's were find out using the USP type I basket dissolution apparatus using basket of 100 mesh size. The dissolution medium was 900 ml of 0.1N HCl (pH 1.2) at 100 rpm at a temperature of 37±0.5°C. Samples of 10 ml were calm at time interval of 5,10,15,20,30, and 60 min, and analyzed using UV visible spectrophotometer at 260 nm [33].

2.2.5 Powder X-Ray Diffraction (PXRD) studies

PXRD patterns of pure LPO, and optimized batch of microwave SD's of were determined employing a diffractometer (Bruker, AXS D-8 Advance SPPU) equipped with a rotating target thermionic tube and a camera lens direction finder. The X-ray supply was Kα radiation from a copper target with black lead monoChromater. The thermionic tube was operated at a possible of 50 kW and a current of 150 mA. The vary (2θ) of scans was from 5° to 50° at a speed of 2° per minute at increments of 0.1° [34-37].

2.2.6 Differential Scanning Calorimetry (DSC)

The thermal behavior of pure LPO, and optimized batch of microwave SD's of were determined using differential scanning calorimetry. 1-2 mg of samples were weighed into aluminum pan and sealed with the lid having a pinhole within the center. Sealed pan-lid was then loaded on DSC instrument and heated from 0°C to 300°C at a heating rate of 10°C/min. Nitrogen was used as the purge gas for the instrument [34-37].

2.2.7 Scanning Electron Microscopy (SEM)

SEM is used to observe sample surfaces. When the specimen is irradiated by a beam of fine electrons (known as an electronic probe), secondary electrons are emitted from the specimen surfaces producing various signals that can be used to obtain information about the surface topography and composition. The surface morphology of the pure LPO and PM powder optimized batch of microwave SD's and were characterized by scanning electronic microscopy (FEI Nova NanoSEM 450 Bruker X Flash 6130) operating at of 10-kV accelerating voltage [34-37].

3. RESULTS AND DISCUSSION

3.1 Compatibility Studies

3.1.1 FTIR analysis

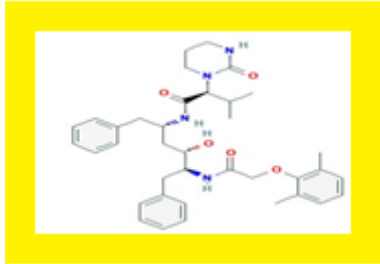
Compatibility studies were performed to reveal and study any possible interaction between the LPO with excipient β -CD. FTIR of LPO (Table 2, Fig. 1) Showed strong characteristic peaks of LPO i.e. Showed the strong characteristic peaks at 1655 cm^{-1} (C=N stretching), 1739 cm^{-1} (C=O stretching ester), also remain present in the PM of LPO with β -CD in a 1:1 ratio indicate no interaction between drug and polymer. Fig. 2 shows the characteristic peaks and functional groups which are present and responsible for the antiviral activity of LPO. In PM characteristic

peaks of LPO also remain present (part -C) with β -CD in a 1:1 ratio indicate no interaction between LPO and β -CD. In case of IR for optimized batch by MWI sample representing regarding the disappearance of characteristics peaks of LPO in SD (D) as compared to pure drugs indicative of the configuration of inclusion complex between drugs and polymer occurs by suggesting that SD of LPO were prepared using MWI method.

3.1.2 Phase solubility studies

The phase solubility diagram was got through by plotting the molar concentration of LPO versus the molar concentration of the β -CD used. Fig. 2 illustrate the phase solubility diagram of LPO with, β -CD.

Table 2. Characteristic peak for LPO infrared absorption bands

Sr. No	Experimental Frequency (cm^{-1})	Characteristic Peak	Structure of LPO
LPO			
01	2957	CH stretching	
02	1739	C=O stretching ester	
03	1655	C=N stretching	
04	1579	C=C stretching alkenes	
05	1204	C-O stretching ester	
β-CD			
01	1447	Overtones or combination bands of -C-C stretching	
02	1199	C-O-C stretching	

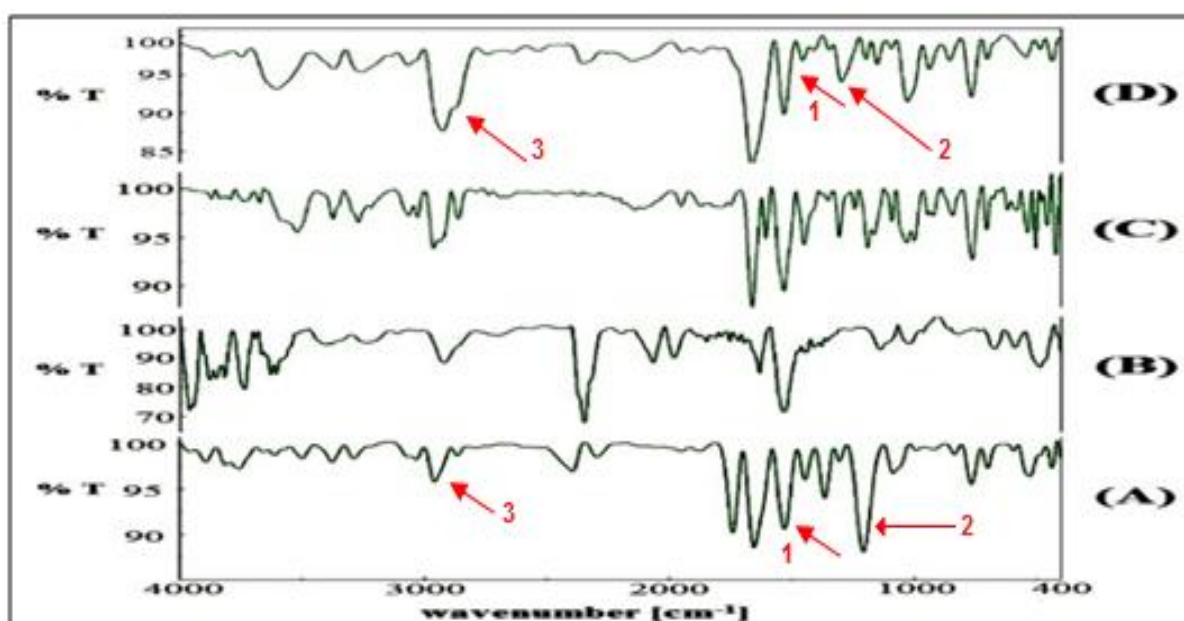


Fig. 1. IR spectra of (A) Pure LPO (B) β CD (C) PM (D) SD-MWI

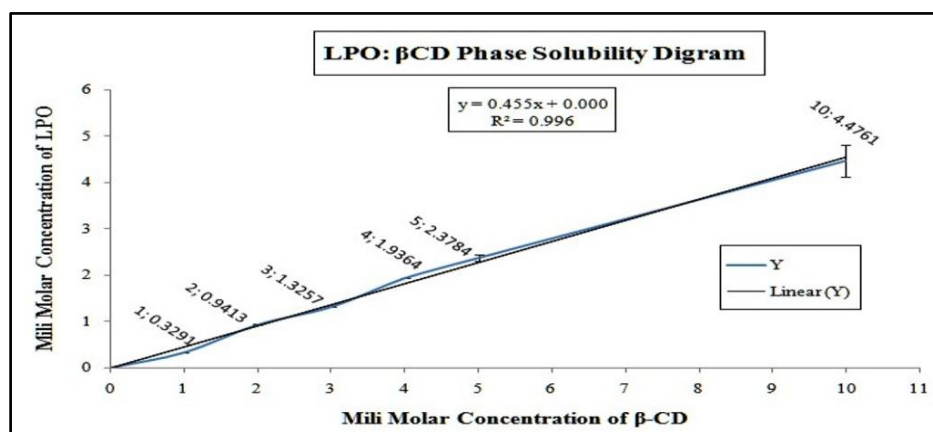


Fig. 2. Phase solubility analysis of LPO with β -CD

The slope of the lines was found to be 0.455 for LPO. The slope for the line is less than unity, it was surmised that the enhance in the solubility was noted because of the formation of a 1:1 molar complex calculated from the slope of the phase solubility diagram were 389 ± 1.45 M⁻¹ for LPO, which pointed toward a appropriate and stable complex formation. Cyclodextrin-drug complexes with K_s values are reported to be in the range of 200 to 5000 M⁻¹ confirm enhanced dissolution properties. Solubility constant (K_c) value for LPO is in the range of reported values, Therefore, a 1:1 ratio of β -CD was selected for LPO for other studies.

3.1.3 Drug content

Table 3 shows the average drug content of LPO in PM was 90.32 %, and in SD prepared by MWI technique it is 84.28 PM and SD showed the presence of more than 80 % of the drug content and less than ± 03 standard deviations from the results. It indicates that the drug is evenly dispersed in the powdered form along with β -CD. Therefore, the method used in this study appears to be reproducible for the preparation of solid dispersion.

3.1.4 Optimization of the MWI SD batches of LPO with β -CD by DoE software

The statistical assessment of dependent variables were carried out by analysis of variance (ANOVA) using DoE version 12. The ANOVA outcome (P value) of the variables on percentage drug dissolved of solid dispersion by MWI technique are shown in Table 4. The comprehensive outline for results of regression analysis of LPO-SD by MWI is revealed in Table 4. The significant parameters in the equations

can be selected using a stepwise forward and backward elimination for the calculation of regression analysis. However, in the present study full model having both significant P values were used in obtaining dependent variables. The coefficients for the equations representing the quantitative effect of the independent variables on percentage drug dissolved in 0.1 N HCl for each factors are shown in Table 5. The equations for factor can be generated by putting values of coefficients in Equation 03.

$$Y = A^0 + A1X1 + B2X2 + A1B2 X1 X2 + A1^2X1^2 + B2^2 X2^2 \quad \text{Equation 03}$$

Since the P-values less than 0.0500 indicates the input value of factors selected for LPO to prepare SD by MWI i.e. Time = 4 min & Power 300 watts as this variable code batch F1 give the higher percentage of drug release that is significant. The small changes in the value of factor effect the study i.e. dissolution rate get affect.

Fig. 3 showing the prediction for % dissolution rate at the dimensions of X1 and X2. The expected worth then compared with the predicted worth of response. These established the closeness in the relationship between the actual and predicted value of the dependent variable. In Fig. 3 prediction response is clear that the factor X1 i.e. Time of exposure increases the dissolution rate response decreases, while another factor X2 i.e. Power exposure as the power is increasing dissolution rate is also increases up to intermediate after that as power value is increases the dissolution rate response is decreases. Thus the actual value (X1 = 4 min, X2 = 300 watt) plotted it shows the resemblance with predicted value.

Table 3. Drug content for PM, SD by solvent and MWI method

Sr. No.	Composition	% Drug Content
		N=3
01	LPO:β-CD (1:1) PM	90.32± 2.5
02	Optimized Batch MWI	84.28 ± 0.36

Table 4. Analysis of variance results (P value) effect of the variables on percentage LPO drug release of solid dispersions by MWI technique

Source	Coefficient Estimate	F-value	p-value
Intercept	47.43	69.43	0.0027
A-Power	-7.98	81.29	0.0029
B-Time	-3.04	7.16	0.0753
AB	5.80	19.12	0.0221
A ²	9.10	38.46	0.0084
B ²	10.16	54.90	0.0051

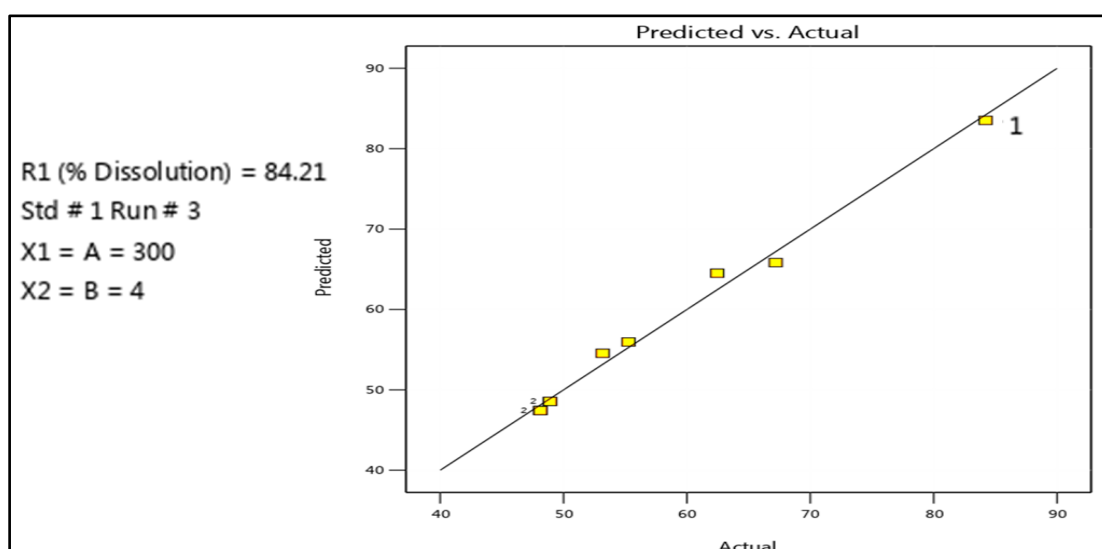


Fig. 3. Predicted v/s actual value of dissolution rate of SD of LPO

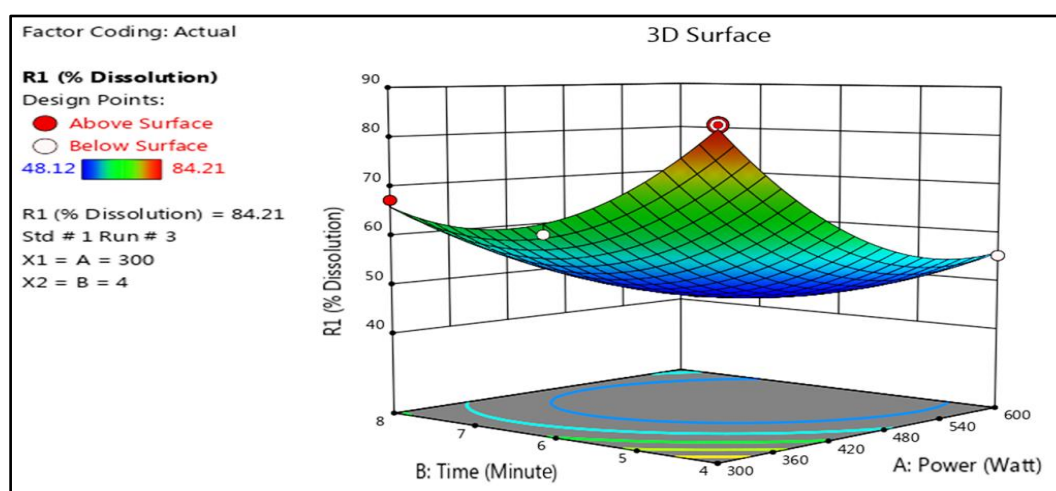


Fig. 4. Response surface plot (3D Surface) of LPO-SD by MWI

From Response surface plot analysis in Fig 4 its concluded that the actual value show the similar response as predict for the model study and the model for experimental design selected is significant. Hence optimized batch (F1 in Table 1 value i.e. X1= 4 min, X2 = 300 watt) is selected with reference of statically model is significant by the design expert software in the preparation of SD of LPO with β -CD in 1:1 ratio by MWI technique.

3.1.5 *In vitro* comparative drug release studies

The comparative study of dissolution profile of LPO, PM along with optimized SDs prepared by MWI technique shown in Figs. 5-A & 5-B. In Fig. 5-A the release profile LPO form all batches are

depicted. From the Fig. 5-A it is clear that all batch F1 shows highest percentage of release of LPO hence selected as optimized batch and compared with plan LPO and PM separately showing in Fig. 5-B. From the Fig. 5-B it indicates that pure LPO has a very low dissolution profile of less than 15 % whereas in the case of PM, the release profile for LPO was about 20%. The SD prepared by MWI technique give more than 80 % release of LPO in 90 min. The carrier used β -CD having cone shape cavity in that LPO particle lodge as because molecular weight of β -CD is 1138 indicates small LPO have molecular weight 629 easily get lodge in the cavity of β -CD and due to which LPO is remain more in concentration available at the time of dissolution hence showing burst release rate.

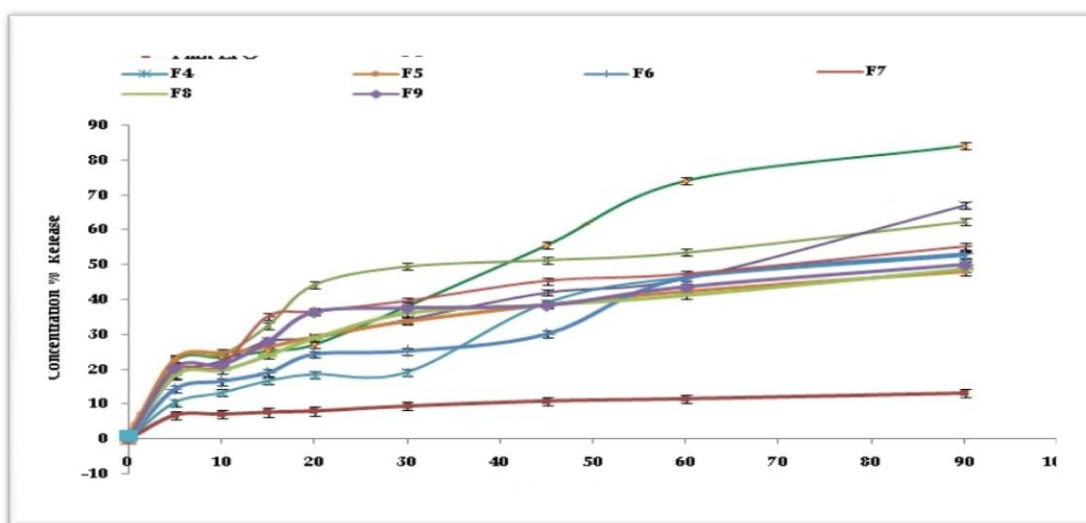


Fig. 5-A. Dissolution profile of All batches SD-MWI LPO

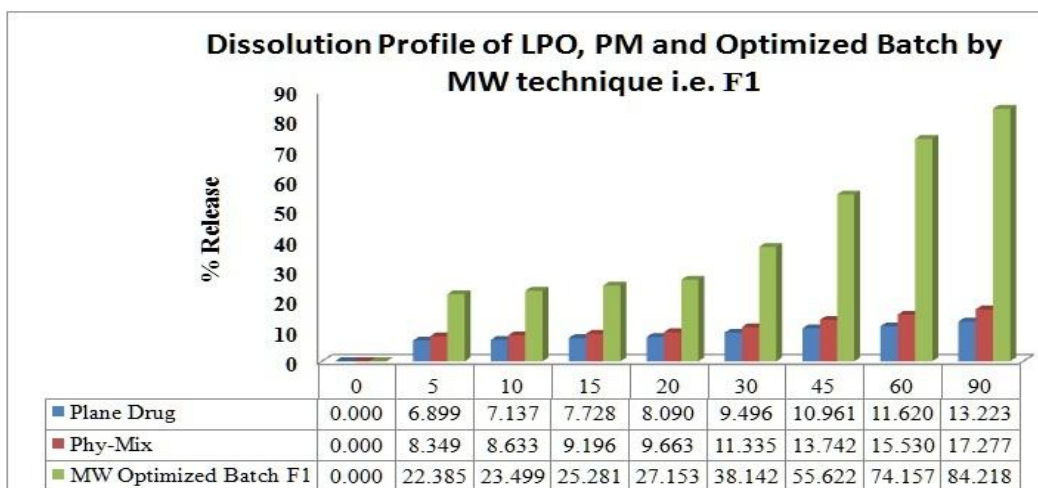


Fig. 5-B. Dissolution profile of LPO , PM & Optimized SDs-MWI prepared by MWI method

3.1.6 PXRD studies

Fig. 6 shows X-ray diffraction pattern for pure LPO showing the distinctive sharp broad peaks of 664, 792, at ~ 25° at 2θ indicating the crystal form of LPO. In PM, these peaks are lower intensity indicating partial crystalline nature as compared to pure drug and in case of SD prepared by MWI of LPO these peaks are totally disappearing of distinctive sharp broad peaks in the similar 2θ angle at ~ 25 indicates the crystal forms of LPO is converted into an amorphous form.

3.1.7 DSC analysis

In Fig. 7 the DSC thermograms of LPO showed a sharp endothermic peak at 123.40°C which is corresponding to their melting point. The thermogram of the PM of LPO slightly shifts with a weak endothermic peak at 122.19°C. The SD prepared by MWI method show shifting of the endothermic peak at 118.22°C. indicates a strong interaction between LPO with β-CD hence confirms complex formation and indicates loss of crystallinity and thus support also with XRD and dissolution studies.

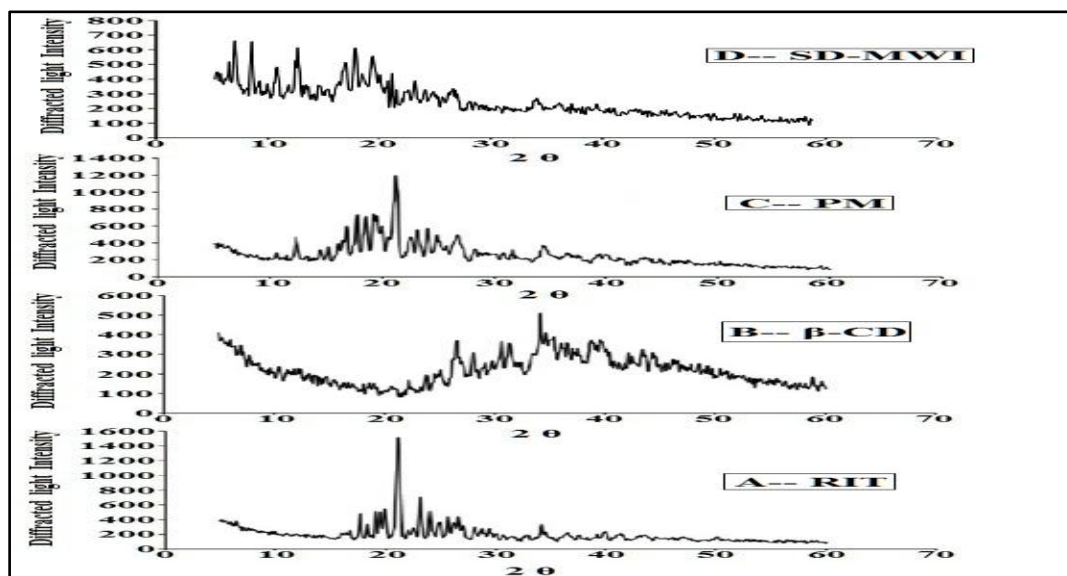


Fig. 6. XRD profile of (A) LPO (B) β-CD (C) PM (D) SD-MWI

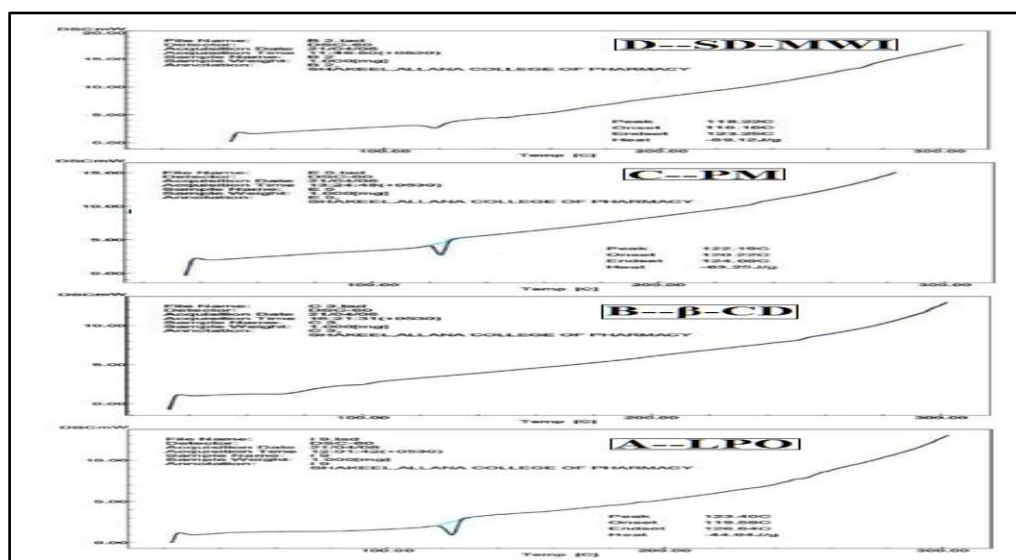


Fig. 7. DSC Thermograms of (A) LPO (B) β-CD (C) PM (D) SD-MWI

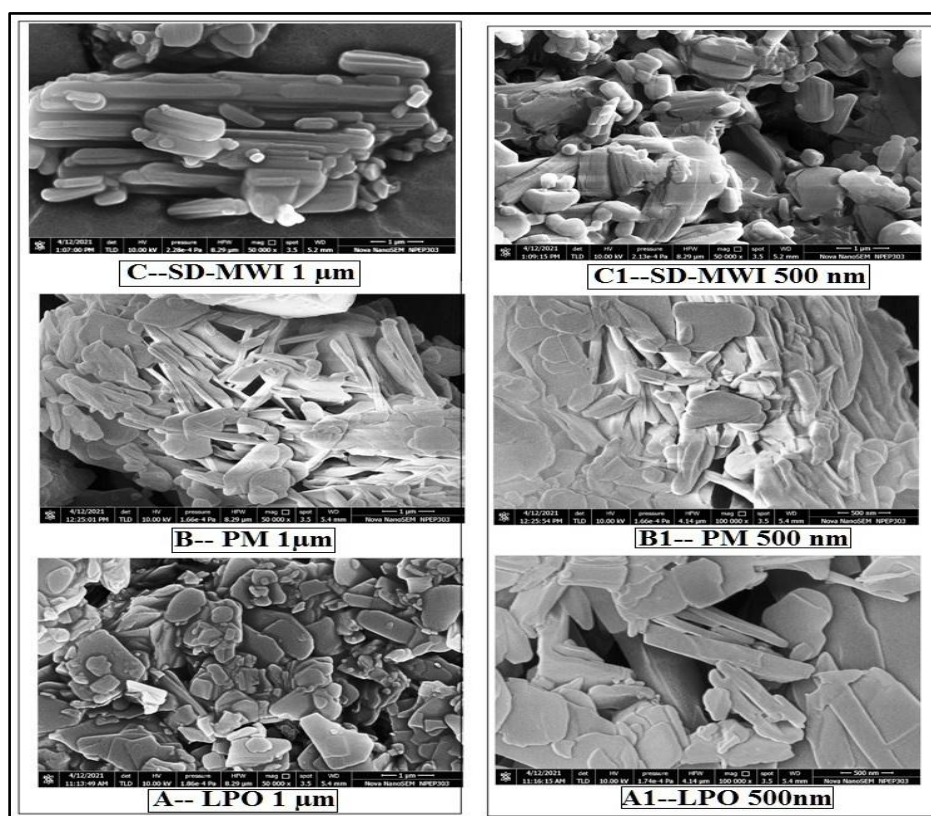


Fig. 8. SEM analysis of LPO (A, A1), PM (B, B1), SD-MWI (C, C1)

3.1.8 SEM analysis

In Fig. 8, SEM shows photomicrographs initial shape of LPO exists in a crystalline cluster rod shape. (A & A1). After the addition of β -CD in 1:1 ratio as a PM, the surface of the rod-shaped particles seemed smooth (B & B1). The morphological analysis for SD of LPO in 1:1 ratio with β -CD prepared by MWI method illustrates smooth edge with loss of rod shape as compared to the pure LPO indicates loss of crystallinity (C & C1), thus supporting with XRD studies.

4. CONCLUSION

The solubility and dissolution release of LPO can be improved through preparation of SD by β -CD. MWI was found to improve dissolution rate to an extent as compare to plan LPO. FTIR and DSC studies depicted that there were no interactions between the LPO and the carrier used. XRD studies specify feasible destruction in the crystal lattice structure of the drug in to amorphous state. SEM studies showed that pure LPO is in crystalline state and SD prepared is irregular form and in amorphous state indicates drug dispersed in carrier. Remarkably SD prepared by

MWI technique avoids the use of organic solvent hence the risk of solvent entrapment along with API is avoided with shorter time of exposure of API to microwave. In addition, the technique is environmentally friendly or further called green chemistry because it does not produce fumigating gas or any hazard by product.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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