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PROPERTIES OF SOLID DISPERSIONS OF PALIPERIDONE IN POLYETHYLENE GLYCOL, COMPARISON OF SOLID-STATE PROPERTIES, IMPLEMENTATION OF FACTORIAL DESIGN AND DISSOLUTION BEHAVIOUR

Sameer H. Lakade[1*], Mangesh R. Bhalekar[2]

[1]Department of Pharmaceutics, Karpagam University, Coimbatore (T.N), India, and Department of Pharmaceutics, Sinhgad Institute of Pharmaceutical Sciences, Lonavala, Pune 410401.

[2]Department of Pharmaceutics, AISSMS College of Pharmacy, Kennedy road, Pune 411001.

*Corresponding Author Email: sameer_patil97@rediffmail.com

ABSTRACT

Paliperidone, a commonly prescribed antipsychotic drug, belongs to class II under BCS and exhibits low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such, its oral absorption is limited by its low dissolution and it requires enhancement of solubility and dissolution for better oral bioavailability. The solid dispersions of paliperidon were prepared by various methods and 2^3 statistical design was applied to the systems to check the influence of various variables on the response factors such as % release and disintegration time. An appropriate statistical model was reached and a significantly enhanced dissolution rate was obtained with the optimized formulation. In conclusion, the statistical model allowed us to understand the effects of formulation variables on the dispersion. The implications of a deeper understanding of the dissolution mechanisms were considered, with particular emphasis on optimizing the choice of carrier and manufacturing method by implementing the statistical design to understand the effects of formulation variables on the dispersion and prediction of stability problems.

KEY WORDS

Factorial design, Solid dispersion, Solubilizer, Paliperidone, Dissolution enhancement.

INTRODUCTION

In 1961, the first approach to use solid dispersions to reduce particle size and to increase the dissolution and oral absorption of poorly water soluble drugs was reported. Other factors that can contribute to the dissolution enhancement from solid dispersions increased by improved wettability[1] and solubility.[2,3] Solid dispersions represent a useful pharmaceutical technique for enhancing the dissolution, absorption and curative efficacy of drugs in dosage forms.[4] Solid dispersion techniques have been used to decrease the particle size of drugs and to increase their dissolution and absorption rates.[5,6] One aspect of solid dispersion that has received little attention is the therapeutic efficacy of the dispersed drug. Theoretically, if the dissolution rate is enhanced, the oral absorption rate should be increased to prove that the absorption process is dissolution rate-limited.[7] For these dispersions containing relatively coarse drug particles, increased drug

content is linked to the increased particle size and decreased dissolution rate.[8] The poor solubility was still a major hurdle in the drug development and clinical use, and various drug candidates had to be abandoned despite favorable pharmacological activity.[9] Although the use of the water soluble carrier in a solid dispersion system may increase drug solubility, to some extent, the provision of sink conditions is still necessary in dissolution testing in order to characterize the factors affecting drug release.[10] It is recognized that amorphous materials can have varying amounts of molecular order, but they lack the extensive range packing order that is characteristic of a crystal.[11] The increase in solubility could eliminate the supersaturation in the microenvironment or reduce the degree of supersaturation, resulting in the prevention or delay of the drug crystallization in the microenvironment.[12] The dissolution rate of the polymer carrier itself may decrease on storage. For example, an amorphous polymer may recrystallize to make a polymer with a higher degree of crystallinity. The incorporated drug may also induce changes in crystallinity of the carrier. In dispersions using PEG as the carrier, both unchanged and decreased dissolution rates have been reported after storage, whereas increased dissolution rates after longer storage times have not been obtained. Unchanged dissolution rates after one year of storage at the ambient temperature have been recorded for drugs dispersed in PEG of different molecular weight.[13] It is commonly accepted that the crystallization conditions have an important impact on the physical state of the resulting dispersions and hence on the dissolution characteristics of these dispersions. Unraveling the relationship between the polymorphic behavior of PEG6000/4000/1500 in a solid dispersion and dissolution characteristics of that solid dispersion, is a real gain to our knowledge of solid dispersions since this has never been thoroughly investigated. [14] The aim of the present study was to enhance the dissolution rate of paliperidone using a solid dispersion technique with various hydrophilic polymers. The melt method, solvent evaporation method, and freeze drying method were used to prepare solid dispersion particles of Paliperidone. Solid dispersion systems and physical mixtures of Paliperidone were established with polyethylene glycol (PEG6000/4000/1500) each at 1:1, 1:3 and 1:5 ratios. The selection of unique ratios of polymers was purely on a random basis. The purpose of the present study was to employ an experimental design to develop an optimization strategy to increase the water dissolution of paliperidone by using carriers such as glycol at various drug/polymer concentrations (ratios). A three-factor, two-level factorial experimental design was employed to determine whether a particular treatment or combination of treatments was satisfactorily significant in influencing system response. Mathematical elaboration of experimental data was carried out by the computer program Design Expert®.

Chemical Name:

(±)-3-[2-[4-(6-fluoro-1,2 benzisoxazol -3 -yl)-1 piperidyl]ethyl] - 6,7,8,9- tetrahydro-9-hydroxy - 2-methyl-4H-pyrido[1,2-a] pyrimidin - 4 – on

Molecular Formula: $C_{23}H_{27}FN_4O_3$

Preparation of solid Dispersion [15,16,17,18]

a) Melt method b) Solvent evaporation c) Freeze drying method

MATERIALS AND METHODS

Paliperidone was obtained as a gift sample from Alkem Laboratories, Mumbai. PEG 6000, PEG 4000, PEG 1500 was purchased from SD Fine chemicals. Other chemicals and solvents used were of analytical grade.

PHYSICOCHEMICAL CHARACTERIZATION

Fourier transforms infrared spectroscopy

The FT-IR spectral measurements were taken at ambient temperature using Shimadzu FTIR spectrophotometer. The samples were prepared by mixing with KBr powder and FTIR spectra were obtained by powder diffuse reflectance technique on FTIR spectrophotometer.[19]

X-ray diffraction (XRD) study

X-ray diffraction patterns were obtained on a Siemans Kristalloflex D-500 diffractometer with Ni-filtered CuKα radiation with a goniometer speed of 1^0 (2ø) /min and a chart speed of 1 cm/ min.[20]

Differential scanning calorimetry

Heat of fusion determinations was made by DSC 20 (Mettler Switzerland). The sample weight was 5mg in all samples. A heating rate of 10°C/ min was employed and the results presented are mean values of four determinations.[21]

Dissolution study

The dissolution tester was equipped with an outer water bath in order to maintain a constant temperature and sink condition. The dissolution study was done at 37.5°C using the basket method at 50 rpm with 900 ml of dissolution medium 0.1 N HCl (pH 1.2). At a predetermined interval, one ml of the medium was sampled and filtered through a membrane filter (0.45µm), and analyzed spectrophotometrically at 227nm, each time replacing with an equal volume of the plain dissolution medium to maintain the sink condition. [22]

RESULTS

Phase solubility studies

The solubility of paliperidone increased as the PEG 6000 concentration increased, while with PEG 4000 & PEG 1500 low improvement in solubility occurred in comparison to solubility with PEG 6000.The enhancement of solubility with PEG is directly related to the increase in the polymer content. This may be attributed to the hydrophilic nature of the carrier. The results indicated an increase in the solubility of the drug with increasing polymer concentrations.

Drug-Excipients compatibility study by FTIR

Compatibility studies were carried out using FTIR spectrophotometer.

The characteristic absorption peaks of paliperidone were obtained at different wave numbers for different samples. FTIR spectroscopic studies were conducted to understand possible drug-carrier interactions. Broadening and smoothing of C-OH stretching vibrations occurred between 3300-3250 cm^{-1} which indicates the conversion of free OH group into the bonded form. The sp^3 C-H stretch, sp^2 C-H stretch between 2850 – 3010 cm^{-1}, C=O (carbonyl group) at 1633 cm-1, C–F stretch at 1112 cm^{-1}, C–O stretch at 980 cm^{-1} are prominently decreased in a 1:5 ratio as compared to 1:1 and 1:3 ratios. The observed FTIR spectra of pure drug paliperidone and solid dispersion as shown in Fig no 2 indicates no significant evidence of chemical interaction between the drug and carrier confirming the stability of the drug in the solid dispersion.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis is commonly used to investigate the structure of solid dispersions and to demonstrate possible drug/matrix interactions through the shape of the peaks, melting temperatures, and the exact melting heat offered by the thermogram. DSC curves of paliperidone for the prepared solid dispersions were obtained by a differential scanning calorimeter DSC 20 (Mettler Switzerland) at a heating rate of 10°C/min from 30°C to 300°C in a nitrogen atmosphere. The DSC thermogram of paliperidone alone showed endothermic T_{max} at 180.05°C, corresponding to the melting point of the crystalline form of the drug paliperidone. Considering the melting point

of polymer curing curve for both polymers using melt method, was observed at 180°C. It may be due to the cross linking of the polymer molecule with drugs. It usually appeared soon after the glass transition temperature. The complete disappearance of drug peak in both system, suggests the solubilization of the drug polymeric matrix and change in crystalline property of paliperidone i.e. conversion of the drug to amorphous form.

DSC spectra of drug

From the spectral evidence of DSC, it can be suggested that this physical change of drug in the solid dispersion is due to decrease in crystalline property of the drug. Because of this, it has contributed to significant improvement of solubility of paliperidone in the solid dispersion.

Data Analysis

The response surface methodology is a set of mathematical and statistical techniques used for modeling and analysis issue in which a response of interest is a function of several variables and the objective is to optimize this response. The run or formulations, which is designed based on factorial designs is evaluated for the response. The response values are always subjected to multiple regression analysis to find out the relationship between the factor used and the response value obtained. The multiple regression analysis was done using Design Expert 9 demo version software, which is specially meant for this optimization process. Analysis of data was carried out using ANOVA study and the individual parameter was evaluated. Using the regression value, coefficient of a factor of the polynomial equation for each response is generated.

Optimization of formulation using 2^3 factorial design

The 2^3 factorial design is one of the tools used to study the effect of different variables on the quality determinant parameters of any formulation. Based on design of experiments, this design was employed to investigate the effect of three independent factors. A 2^3 factorial designs for three factors at two levels was selected to optimize the varied response variables. The 2^3 factorial design was applied to study the effects of formulation variables such as the amount of light MgO, sodium lauryl sulphate, crospovidone XL-10 on the response factors such as % release at desired time and disintegration time. In this design, three factors are assessed, each at two levels. Experimental trials were made with all eight possible combinations. All other formulation variables and processing variables of the study were kept invariant throughout the study. Statistical analysis of the 2^3 factorial design batches was performed.

Figs. 6 and 7 show the dissolution behavior of paliperidone in its solid dispersion. The release rate profiles were drawn as the percentage dissolution of paliperidone from the solid dispersion and the pure drug versus time. Dissolution studies of pure paliperidone and all other prepared formulations implemented by factorial design in batches (A1- A8) were carried out in 0.1N HCl. T80% (time to dissolve 80% drug) values were derived from the release profile. Dissolution of paliperidone from its physical mixtures was slightly higher than that of the pure drug, but maximum improvement in the dissolution rate was observed with lyophilized mixtures. To optimize the percent paliperidone release, mathematical relationships were generated between dependent and independent variables. This resulted in polynomial equations for dissolution after 60 min in terms of coded factors which are as follows:

Final equation in the terms of coded factors:

Disintegration time = 188.13 + 6.83A - 9.83B - 39.38C

Final equation in the terms of actual factors:

Disintegration time = 260 + 1.37 (Light MgO) - 3.75 (Sodium Lauryl Sulphate) -2.62 (Crospovidone XL-10)

Positive sign for the coefficient of factor A indicates that increase in the factor A concentration will increase the DT. Negative sign for the coefficient of factor B and C indicates that an increase in the factors B and C will decrease the DT. Generating the respective model equations, allows the selection of the best formulation experimentally prepared, and also of the best formulation within the experimental range. The selected optimized formulation was prepared and the observed values were deemed to be quite comparable to the predicted values.

CONCLUSION

This article has outlined some of the current findings with regard to the mechanisms by which drugs may be released from solid dispersions, focussing on the solid state properties of dispersions and the possible fate of drug particles within a solid disperse matrix. The dissolution rate of paliperidone from solid dispersions with PEG 6000 was markedly increased in comparison to pure paliperidone in physical mixtures. We assume that the main reason for dissolution rate enhancement was improved wetting of paliperidone crystals owing to attachment of PEG 6000 particles on the surface. All other mechanisms can be excluded since solid-state characterization did not reveal any change in the paliperidone crystal structure and the size of the paliperidone particles was preserved. Overall, solid dispersions provide the industry with some extremely exciting possibilities with regard to the formulation of poorly soluble drugs. Still, the fundamental behaviour of these systems will limit the utility of this approach and at best will remain empirical.

Factor	Name	Units	Type	Actual values		Coded values	
				Low	High	Low	High
A	Light MgO	Mg	Numerical	30	40	-1	+1
B	Sodium Lauryl sulphate	Mg	Numerical	5	10	-1	+1
C	Crospovidone XL-10	Mg	Numerical	20	50	-1	+1

Table No 1. Variable level of factorial design

Response	Description	Observations	Min	Max	Mean
Y1	% Release	8	93.6	98.9	96.39
Y2	Disintegration time (secs.)	8	130	240	188.125

Table No 2. Various responses for factorial design

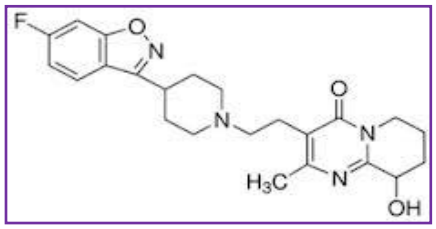

Fig No 1: Chemical structure of paliperidone

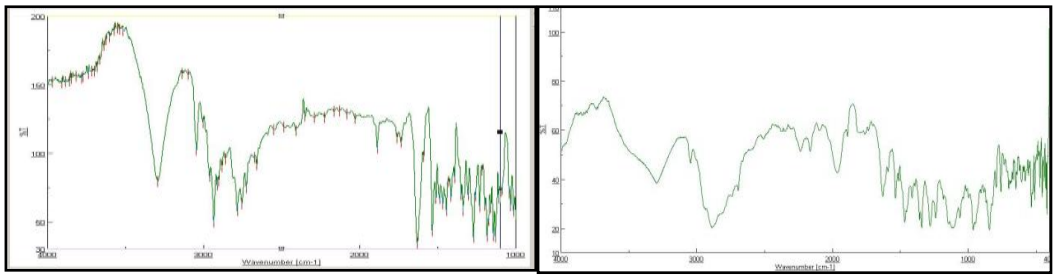

Fig No 2: FTIR spectra a) paliperidone b) solid dispersion

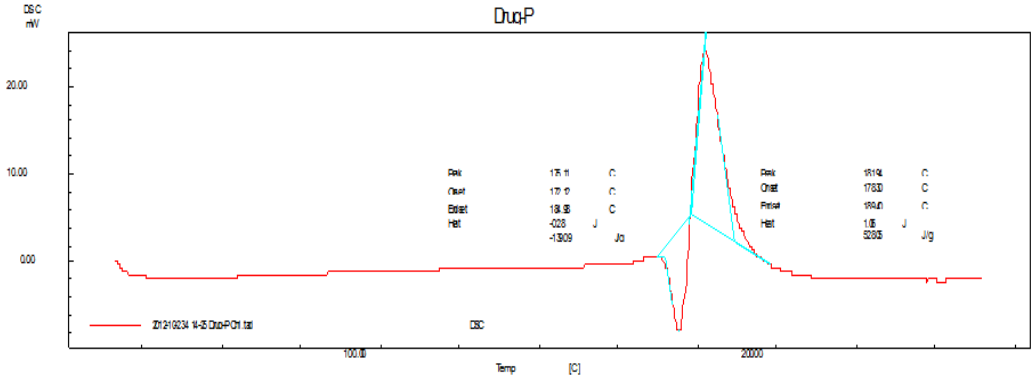

Figure No 3: DSC spectra of drug

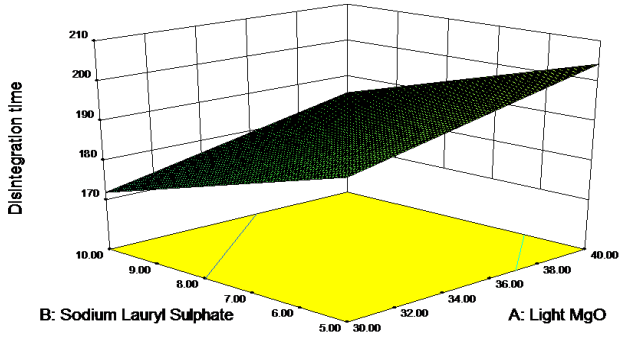

Figure No. 4: 3D plot for disintegration time crospovidone level is constant

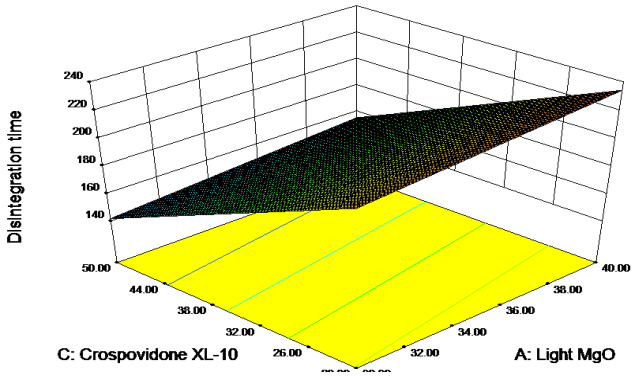

Figure No.5. 3D plot for DT when SLS level is constant

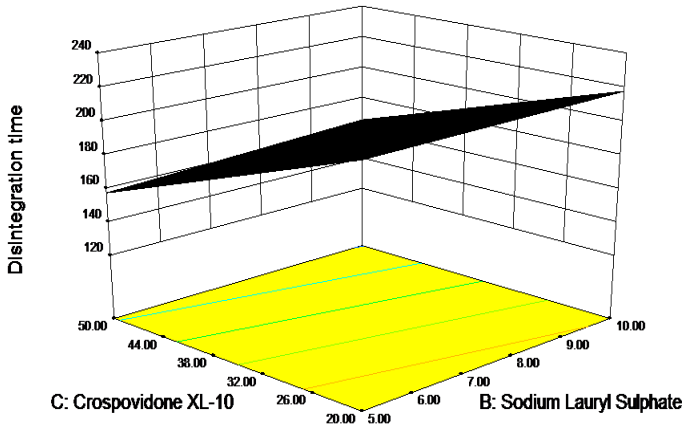

Figure No. 6.3D plot for DT when light MgO level is constant

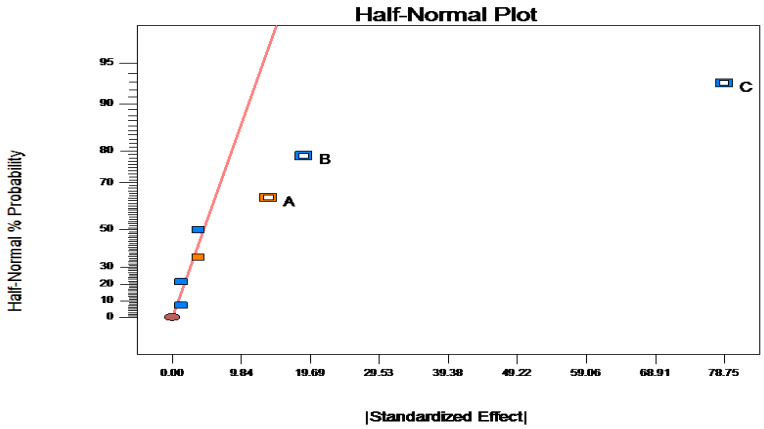

Figure No.7. Half normal plot for disintegration time

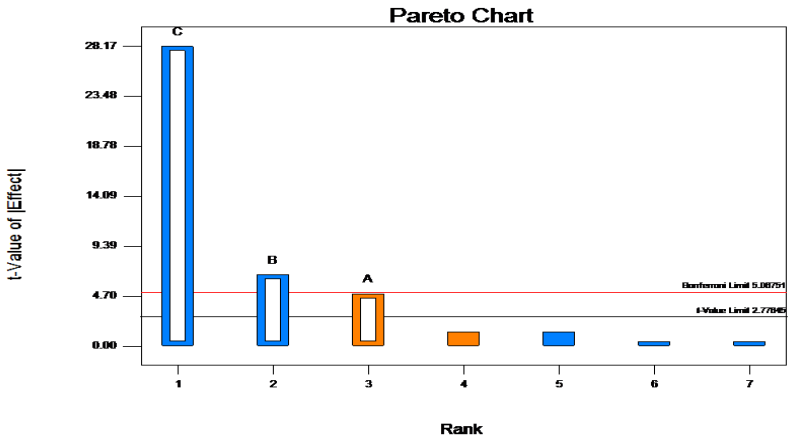

Figure No. 8. Pareto chart for disintegration time

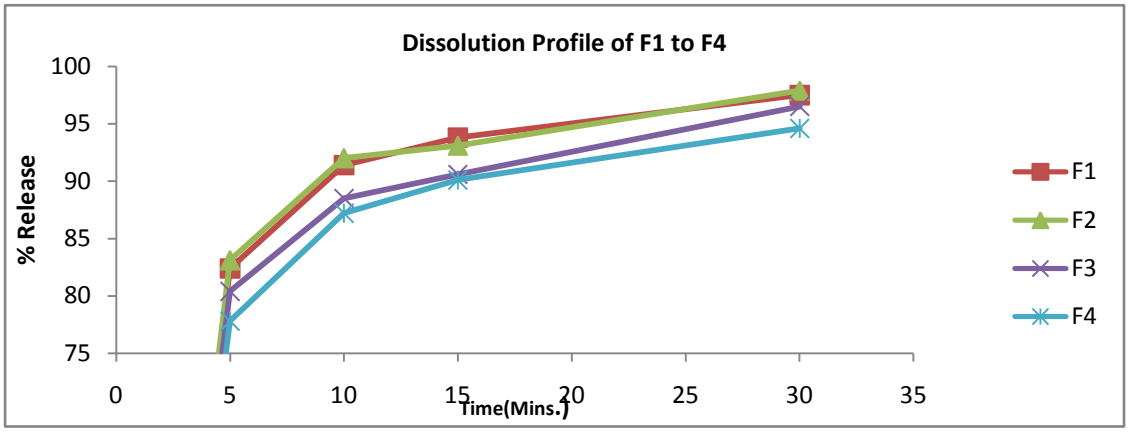

Figure No.9: Dissolution profiles of preliminary trials F1 to F4

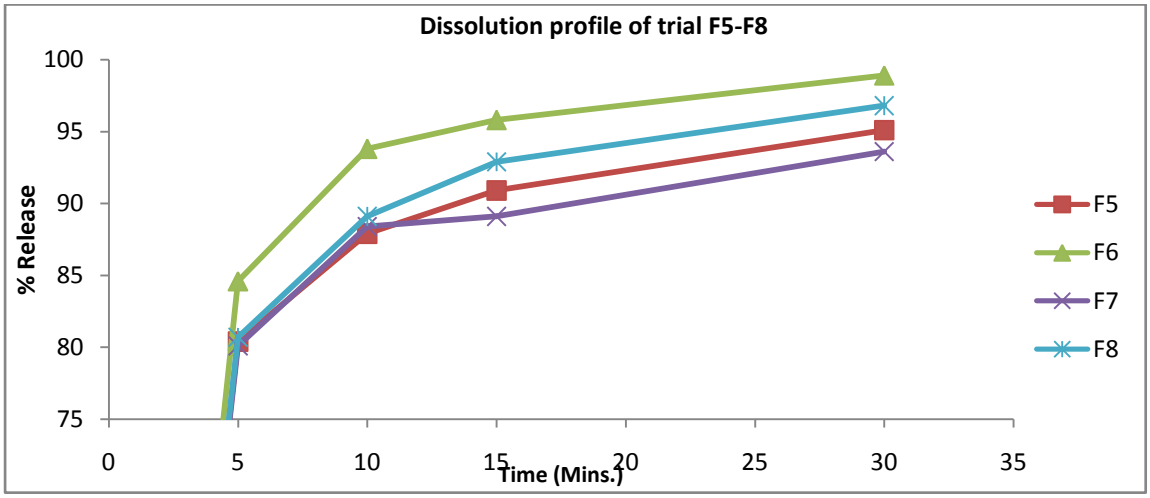

Figure No. 10: Dissolution profiles of preliminary trials F5 to F8

Competing interests

The authors report no competing interests. The corresponding author alone is responsible for the content and writing of the paper.

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***Corresponding Author:**
Mr. Sameer H. Lakade
Department of Pharmaceutics,
Sinhgad Institute of Pharmaceutical Sciences,
Lonavala. Pune-410401
E -mail: sameer_patil97@rediffmail.com