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Formulation and Physicochemical Characterization of Novel Oral Films for Mucosal Drug Delivery System in the Treatment of Schizophrenia

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SHUBHANGI DASWADKAR, ASHVIN BHOGE*

Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharastra, India

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ABSTRACT

The main aim of the present work was to formulate fast dissolving oral films of paliperidone. Paliperidone is a second-generation antipsychotic drug that is used for the treatment of schizophrenia and has low aqueous solubility and bioavailability. This drug also undergoes first-pass metabolism. To overcome all these problems fast dissolving oral films were prepared which helps to improve the bioavailability of drugs. Oral films dissolve fastly along with drugs and mostly all drug absorbs through oral mucosa in the systemic circulation. Oral films were prepared by the solvent casting method. HPMC, PEG 400, and saliva stimulating agents were optimized by using central composite 3 factor, 2 level design based on drug release, and thickness of films. A total of nineteen batches were prepared from which batch containing 50% HPMC, 20% PEG, and 6% saliva stimulating agent was found to be best. Oral films of the optimized batch were disintegrated within 13 sec and show 98.9% drug release. The optimized film was further evaluated for drug content, folding endurance, tensile strength, and physical appearance.

INTRODUCTION

The oral route of drug administration has wide acceptance of total dosage form due to ease of ingestion, pain avoidance, patient compliance. Fast dissolving oral films that dissolve/disintegrate in the mouth within a few seconds without the addition of water. Therefore they are suitable for both pediatric and geriatric patients. Oral strips and oral films which rapidly dissolve under the tongue or buccal cavity could also improve the dissolution of the poorly soluble drug. [1,2]

In the formulation of Mouth dissolving film of paliperidone HPMC and PEG400 use as film-forming polymer and plasticizer respectively and it also play the important role in the mouth dissolving film of paliperidone, HPMC and PEG400 are also use for the enhance the solubility of the poorly water-soluble drug. And hence it also improves the drug release percentage. Citric Acid is used as a stimulating agent and methanol is used as a vehicle.[5,8,11]

Fast dissolving films, a type of oral drug delivery system for the oral delivery of the drug, was developed based on the technology of the transdermal patch. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.[1,2]

Paliperidone (PLP) is a second-generation atypical antipsychotic drug indicated for the acute and maintenance treatment of schizophrenia in adults. The PLP is practically insoluble in water. The low aqueous solubility of the drug decreases the bioavailability of the drug. Paliperidone is a primary active metabolite of the antipsychotic drug risperidone. Schizophrenia is a disorder that may result in some combination of hallucinations, delusions, and extremely disordered thinking. Administration of paliperidone oral films is a preferred and convenient route of administration.[3]

MATERIALS AND METHOD

MATERIAL:

Paliperidone (PLP) powder obtained as a gift sample from Wockhardt Ltd.Hydroxypropyl methylcellulose (HPMC E3). Citric acid, Sodium lauryl sulfate (SLS), Polyethylene glycol (PEG 400), Methanol ware obtained from the college laboratory.

METHOD:

Preparation of mouth dissolving film:

The mouth dissolving film of Paliperidone (4 mg/film) was prepared by the solvent casting method. In which HPMC as film former. PEG 400 as a plasticizer, Saliva Stimulating agent, and flavoring and sweetening agent was added.[8,16]

Method of Preparation:

First HPMC was weighed and dispersed in solvent i.e water with help of stirrer to form a homogenous clear solution. The required quantity of plasticizer (PEG-400) and drug (Paliperidone) were added to ethanol stirred for 1 hr. After that, this solution and other excipient were added to the polymer solution and properly stirred to get a clear solution. Then the solution was degassed in fornicator for 10 min. The bubble-free solution was poured in Petri plate and dried it. Film after drying was removed and cut in the desired size. The composition of formulation as per the factorial layout as shown in table no 2. [8,16]

Drug Excipient capability study:

Fourier Transform Infrared Spectroscopy Study: FTIR Spectrum of API of Paliperidone and the other excipient use in the preparation of Paliperidone MDFs was recorded. The sample was analyzed by the KBr method using FTIR spectroscopy. About 10 mg of a formulation is mix with dried KBr in equal quantity. The mixture with properly mix using mortar and pestle. Then powder was scanned over the frequency range.

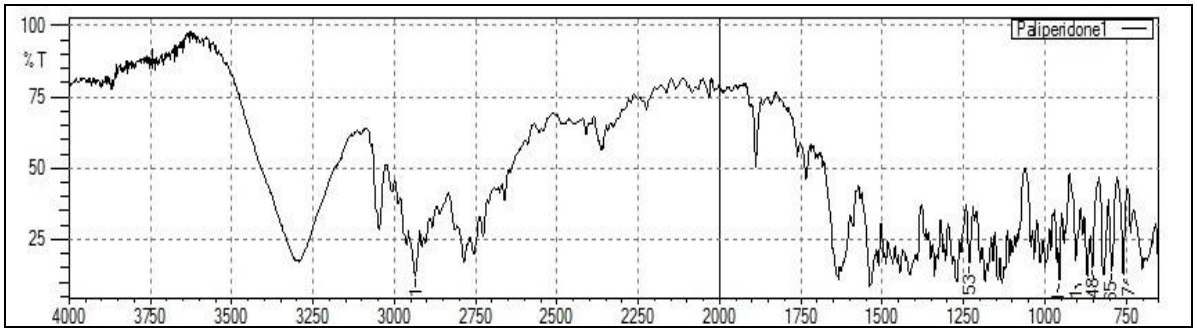

Figure No. 1: FTIR spectrum of PALIPERIDONE

Table No. 1: Functional group and wavenumber

Functional group	Wavenumber cm^{-1}
759	C-H Out of plane
795	CH Blending
958	C=C Blending
1232	C-O Stretching
2935	OH Stretching

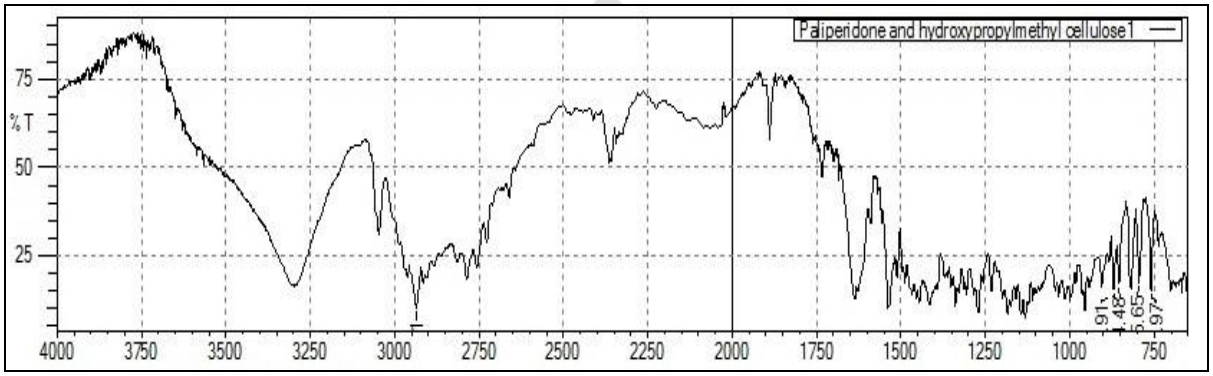

Figure No. 2: FTIR spectrum of Palperidone, HPMC, and other excipients.

The above peaks are considered as characteristics peak of Paliperidone. These peaks were not affected and prominently observed in IR-spectra of drug and excipients. This demonstrates there is no interaction among drug and excipients.

Formulation of Mouth Dissolving Film of Paliperidone:

Optimization by Central Composite 3^2 Factorial Design: A 3^2 randomize full factorial design used in the present study. In this design, 2 factors were evaluated each at 3 levels, and experimental trials were performed at all 19 possible combinations, film Thickness and Drug release (%DR) in 5 min were selected as the dependent variable. Three independent factors

the concentration of Polymer, Plasticizer, and Saliva Stimulating Agent were set two-level; each factor coded as -1 and+1, respectively shown in table no 1.

The actual formulation design of Mouth Dissolving Film Of Palperidone according to full factorial design (3^2) Layout as shown in table no 2.

Table No. 2: Formulation Factors, Concentration, and Levels

Factors	Polymer		Plasticizer		Saliva Stimulating Agent	
Concentration (%)	40	50	5	20	3	6
Levels	-1	+1	-1	+1	-1	+1

Table No. 3: Formulation layout as per the Factorial design

BATCH NO	POLYMER (%) HPMC	PLASTICIZER (%) PEG 400	SALIVA STIMULATING AGENT (%) SLS
F1	36.591	12.5	4.5
F2	40	20	6
F3	50	5	3
F4	45	12.5	7.02
F5	50	20	3
F6	45	12.5	4.5
F7	45	12.5	4.5
F8	45	12.5	4.5
F9	45	12.5	1.97
F10	50	5	6
F11	45	0	4.5
F12	50	20	6
F13	45	12.5	4.5
F14	45	25.1134	4.5
F15	40	5	3
F16	45	12.5	4.5
F17	40	5	6
F18	40	20	3
F19	53.409	12.5	4.5

Evaluation parameter of mouth dissolving oral film

Morphological properties: Properties such as homogeneity, color, transparency, and surface PALIPERIDONE MDFs were tested usually. All the formulation is stored at room temperature. The films were packed in aluminum pouches.[14]

The thickness of the Film: The thickness of the film was measured by micrometer screw gauge with a range of 0-10 mm and revolution 0.001 mm Anvil of the thickness gauge was turned and the film was inserted after making the pointer was set to zero. The estimation was completed in triplicate.[4,13,12]

***In-vitro* disintegration study:** There are several official methods available for the disintegration test. The required size of the film (2cm Diameter) was the place in a beaker containing 10ml distilled water. The disintegration time was noted which was the time when the film started to break or disintegrate. All studies were completed in triplicate for each batch.[10,14]

pH Value: The pH value was determined by dissolving film in 10ml distilled water and the pH of the obtained solution was measured. All determination was performed in triplicate. Film must have a nearly uniform pH value.[18]

Folding Endurance: Folding endurance of the film is essential to study the elasticity of the film during storage and handling. The folding endurance of the film was determined by repeated folding one film at the same place till break. These consider revealing good film properties. A film (2cm Diameter) was cut evenly and repeatedly folded at the same place until it breaks. All determination was performed in triplicate.[9,19,20]

Percent elongation: At the point when stress is applied to the film test extends and alluded to as a strain. Generally, elongation of the film increase as the plasticizer concentration increases. The percentage elongation of the film was determined by the following formula.[4,15]

$$Percent\ elongation = \frac{Increase\ in\ length\ of\ film \times 100}{Initial\ length\ of\ film}$$

Drug Content uniformity: Drug content was determined by dissolving the film containing 4mg of drug dissolved in 100ml water to get 20µg/ml solutions. An aliquot of 2 ml sample

was withdrawn and diluted to 10ml with water. Then the solution was filtered through Whatman filter paper and analyzed by UV-Spectrophotometer at ʎ max of a drug. Content uniformity studies were carried out in triplicate for each batch of the film.[4,15]

***In-vitro* Dissolution Studies:** Paliperidone Mouth dissolving films drug release studies were determined by Franz Diffusion Cell Apparatus having external diameter is 3 cm, internal diameter is 2.8cm, the height of diffusion cell apparatus is 8cmand volume is 30ml. The receptor compartment maintained at 37ºC was continually stirrer at 100rpm. Sample of 1ml was withdrawn at a predetermine time interval over a 30min and replace with an equal volume of the dissolution medium equilibrated at the same temperature. The drug concentration of the withdrawn sample was determined by UV-Spectrophotometer at 238 nm. All studies were carried out in triplicate for each batch of the film sink conditions were maintained throughout the study.[21]

Table No. 4: Evaluation Parameter of MDFs of Paliperidone

Formulation Batches	Thickness of Film (mm)	pH Value	Percent Elongation (%)	Folding Endurance	DRUG Content (%)	Disintegration Time (Sec)	Drug Release (%)
F1	0.16	6.53	2.34	110	90.5	10	60.66
F2	0.17	6.48	2.54	120	96.8	9	78.3
F3	0.18	6.95	2.46	110	95.5	11	37.6
F4	0.18	6.85	1.22	110	95.5	11	68.2
F5	0.20	6.66	3.44	120	80.3	12	34.00
F6	0.18	6.55	3.56	125	85.5	12	67.73
F7	0.18	6.55	3.56	125	85.5	12	67.73
F8	0.18	6.55	3.56	125	85.5	12	67.73
F9	0.18	6.34	1.20	120	80.5	12	52.2
F10	0.19	6.46	1.25	135	80.6	12	68.23
F11	0.18	6.82	2.34	100	82.5	12	47.2
F12	**0.20**	**6.83**	**1.23**	**135**	**99.1**	**13**	**98.99**
F13	0.18	6.76	1.10	108	90.5	14	67.73
F14	0.19	6.88	2.24	120	95.5	12	75.56
F15	0.17	6.46	2.45	125	96.9	11	85.6
F16	0.18	6.55	3.26	125	97.9	12	67.73
F17	0.17	6.99	3.13	140	90.0	11	23.22
F18	0.18	686	1.26	100	97.8	11	75.55
F19	0.20	6.20	1.25	120	95.5	12	65.23

RESULT AND DISCUSSION

Morphological properties of mouth dissolving film: Mouth dissolving film of Paliperidone was observed as color is whitish, transparency is blurred and the surface of the film is plane surface. All formulation is stored at room temperature and packed in aluminum pouches properly.

Optimization

After all evaluation and observational nineteen batches were prepared. According to design expert software the batch no F12were optimize it containing 50% HPMC, 20% PEG, and 6% saliva stimulating agent was found to be best. Oral films of the optimized batch were disintegrated within 13 sec and show 98.9% drug release and it gives effective results.

Evaluation of optimized batch

Response 1: Drug release

The **Model F-value** of 30.39 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case, B, C, AC, BC are significant model terms.

Drug Release = 1466.05771 – 6.23945 *HPMC* 0.273129 *PEG400* – 117.86262 *Citric acid* – 0.059567 *HPMC*PEG400* + 2.58750 *HPMC*Citricacid* + 1.10544 *PEG400*Citric acid* – 0.0054405 $HPMC^2$ – 0.034017 $PEG400^2$– 1.05585 $Citric\ acid^2$

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. In this study shows the concentration of polymer and plasticizer i.e HPMC and PEG400 increase the drug release is also increases and it showed higher drug release percentage.

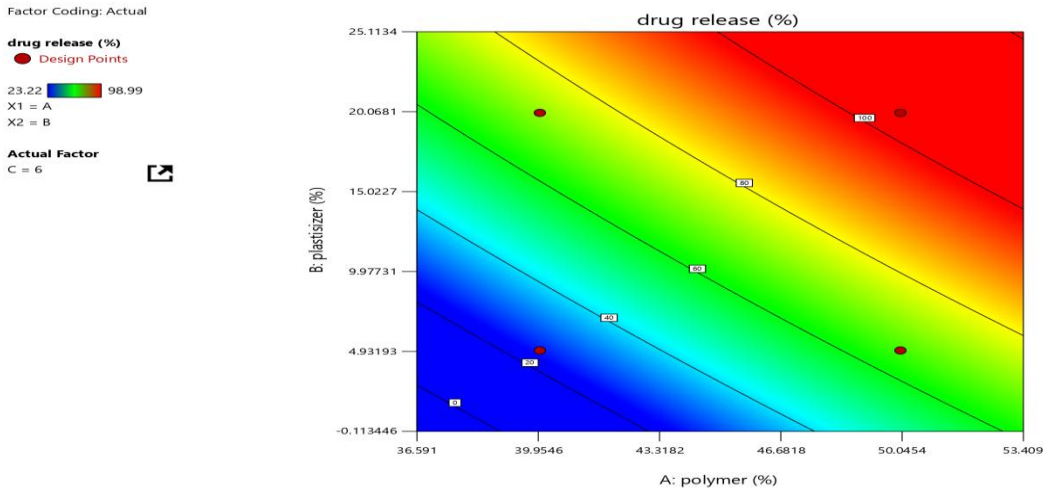

Figure No. 3: Counter plot of effect of concentration of Polymer and plasticizer on Drug Release

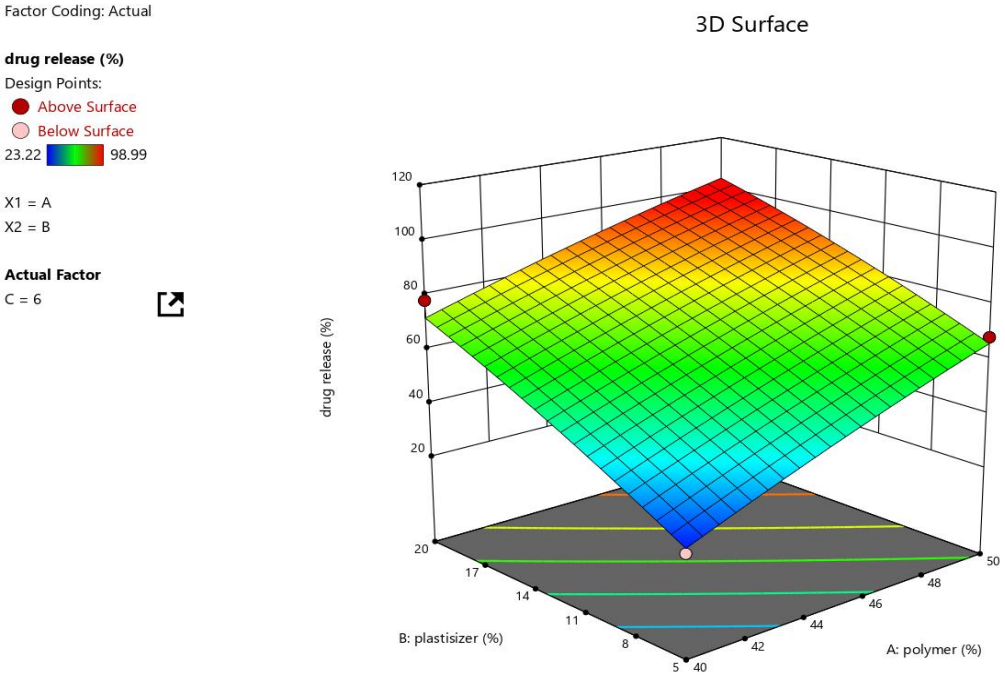

Figure No. 4: 3D Graph for Effect of Concentration Polymer and Plasticizer on Drug Release

Response 2: Thickness

The **Model F-value** of 74.49 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case, A, B, AB, AC, BC, B^2 are significant model terms.

Thickness = 0.187880 – 0.000739 *HPMC* – 0.002300 *PEG400* – 0.012847 *Citric acid* + 0.000067 *HPMC*PEG400* + 0.000333 *HPMC*Citric acid* – 0.000222 *PEG400*Citric acid* + 6.24518E – 06 $HPMC^2$+ 0.000034 $PEG400^2$ + 0.000069 $Citric\ acid^2$

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. In these study shows the concentration of polymer and plasticizer i.e HPMC and PEG400 is increases the Thickness of film.

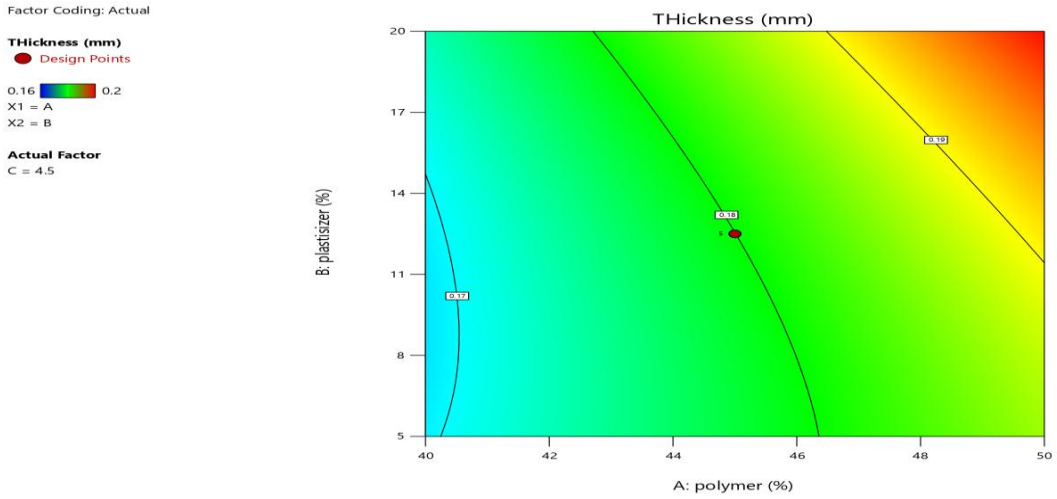

Figure No. 5: Counter Plot of Effect of Concentration of Polymer and Plasticizer on Thickness of Film

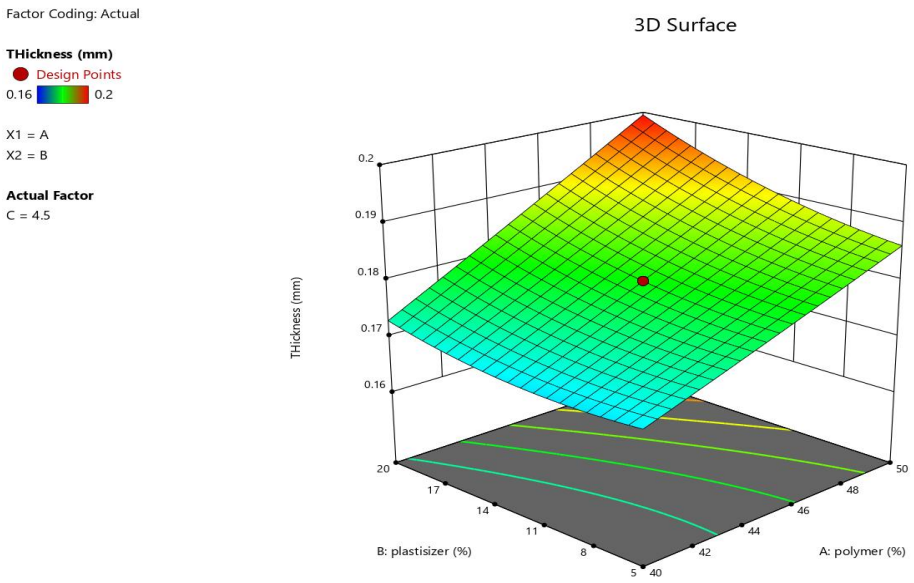

Figure No. 6: 3D Graph Effect of Concentration of Polymer and Plasticizer on Thickness of Film

Stability study:

The stability studies of the optimized batch F12 was carried out at 40 ± 2^0C temperature with 75±5% RH for 3 months and showing data for Thickness, Disintegration time, Drug content, Drug release, pH value as shown in table number 5.

Table No. 5: Result of Stability studies of Optimized Batch F12

Sr. No.	Parameter	Initial	1 Month	2 Month	3 Month
1	Thickness (mm)	0.20	0.20	0.20	0.19
2	pH Value	6.8	6.8	6.8	6.8
3	Disintegration time (sec)	13	14	14	14
4	Drug Content (%)	99.1	99.00	98.7	98.6
5	Drug Release (%)	98.9	98.7	98.4	97.8

CONCLUSION

This study discusses the formulation and evaluation of mouth dissolving oral films of paliperidone. Design expert software (central composite) was used to optimize and response surface plots and contour plots were drawn. Polynomial mathematical model (quadratic), generated for various response variables. Formulation F12 was selected by design expert software which exhibits disintegration time of 13 sec and drug release 98.9% within 30 min.

As per the observation concentration, polymer and plasticizer affect the drug release of drugs when the concentration of polymer and plasticizer is increased it also increases the drug release percentage and it shows that also the solubility is increased according to drug release data. This novel approach to the formulation may be helpful to increase drug release percentage.

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