Research Article

Formulation and Characterization of Daprodustat Orodispersible Film Using 3^2 Factorial Design: *In Vitro* and *Ex Vivo* Evaluation

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ABSTRACT

Daprodustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor used in the management of anemia associated with chronic kidney disease. The present study aimed to develop a chemically and physically stable orodispersible film (ODF) of Daprodustat to enhance solubility, dissolution, and patient compliance. Daprodustat co-precipitates were prepared by the solvent evaporation method using different molar ratios (1:0.5, 1:1, 1:2, 1:3, and 1:4). The prepared co-precipitates were evaluated for solubility, drug content, percentage drug release, FTIR, and DSC analysis. Among all formulations, batch SE3 (3.5577 ± 0.035) demonstrated superior solubility and dissolution and was selected for ODF preparation. Orodispersible films were prepared by the solvent casting method using polymers such as HPMC E5, HPMC, and PVA at different concentrations, with PEG 400 and propylene glycol as plasticizers, along with other suitable excipients. Preliminary evaluation indicated that formulation F10 exhibited the highest drug release (79.61%) and satisfactory tensile strength (2.2 ± 0.54). Further optimization was carried out using a 3^2 factorial design. Among the optimized batches, batch B2 showed maximum drug release (96.45%) and improved tensile strength (3.8 ± 0.54). The contour batch demonstrated enhanced ex vivo permeation (87.02%), confirming the significant influence of polymer concentration on drug release. Short-term stability studies of the optimized batch B2 at 40 ± 2°C and 75 ± 5% RH indicated good stability. The developed ODF of Daprodustat provided immediate drug release, bypassed first-pass metabolism, reduced dosing frequency, and improved patient compliance.

Keywords: Daprodustat, orodispersible Film, Renal Treatment, In vitro Drug release, Ex vivo Permeation Study, 3^2 Factorial design.

INTRODUCTION

Oral administration remains the most widely accepted and commonly used route for drug delivery among the general population. It is highly preferred by pharmaceutical manufacturers due to advantages such as improved patient compliance, ease of self-medication, accurate dosing, non-invasive administration, flexibility in formulation, effective pain management, and cost efficiency. Additionally, this route may reduce first-pass metabolism, avoid pre-systemic degradation in the gastrointestinal tract (GIT), and, depending on the drug, benefit from favorable enzymatic conditions that enhance absorption.

Among advanced oral dosage forms, oral disintegrating systems are particularly favored for their convenience and ease of use. Their versatility, compact size, and rapid action have significantly increased their popularity. In recent years, transmucosal drug delivery systems have gained attention as they help overcome the limitations associated with conventional oral administration. Fast-dissolving technologies, including orally disintegrating tablets (ODTs) and oral thin films (OTFs), are increasingly recognized as patient-friendly alternatives for delivering pharmaceuticals and nutraceuticals. The rich blood supply and large surface area of the oral mucosa contribute to improved bioavailability and efficient systemic drug absorption. Orodispersible films (ODFs) are thin polymeric strips, typically 5–20 cm^2 in area, that rapidly disintegrate in the oral cavity, with the drug uniformly dispersed within a hydrophilic polymer matrix.

The solvent evaporation or solvent casting method is widely employed for ODF preparation, particularly for heat-sensitive drugs and small-scale manufacturing. Co-precipitation is another important technique used to enhance the solubility and bioavailability of poorly water-soluble drugs. It involves forming a solid dispersion of the active pharmaceutical ingredient with a suitable carrier, often resulting in an amorphous and more soluble form that improves dissolution.

Anemia associated with chronic kidney disease (CKD) is primarily caused by reduced renal production of erythropoietin and altered iron metabolism due to chronic inflammation. Recent evidence links decreased erythropoietin levels to the downregulation of hypoxia-inducible factor (HIF), a transcription factor responsible for regulating erythropoietin gene expression.

ODFs provide considerable advantages for CKD patients, especially in enhancing medication adherence. Patients with CKD frequently experience polypharmacy and swallowing difficulties, leading to poor compliance and adverse outcomes. Since ODFs dissolve rapidly in the mouth without requiring water, they are particularly beneficial for patients with dysphagia or limited water access. By simplifying drug administration and improving convenience, ODFs can enhance treatment adherence and overall therapeutic effectiveness in CKD management.

Differential Scanning Calorimetry (DSC) analysis

Differential Scanning Calorimetry (DSC) analysis was performed to investigate phase transitions during the formation of the complex and the final formulation. A noticeable shift in the thermogram was observed for the Daprodustat–β-cyclodextrin complex compared to the pure drug. The characteristic endothermic peak of the complex appeared at 237°C, while the orodispersible film exhibited a peak at 230.45°C. These shifts in melting endotherms indicate the occurrence of non-covalent interactions between the drug and the conformer, suggesting the formation of a co-crystal or inclusion complex. Similar non-covalent interactions were also evident in the film formulation. The interaction is primarily attributed to hydrogen bonding between the polar functional groups of the drug and the conformer

MATERIALS AND METHODS

MATERIAL

Daprodustat was obtained as a gift sample from the AMI LIFESCIENCE PVT. LTD. Vadodara, Gujarat. All other excipients were of analytical grade.

METHOD

Preparation of co-precipitate for solubility enhancement:[6]

Drug and beta-cyclodextrin were mixed in different molar ratios and dissolved in methanol and water. Solution was kept on a magnetic stirrer for complete dissolution of mixture. Then, solution was left overnight for complete evaporation of solvent. The resultant mass is pulverized and passed through sieve no.80 and stored in a desiccator.

Polymer dissolved in distilled water and kept on magnetic stirrer for 1 hr. Then Daprodustat co-precipitated dissolved in plasticizer and their solution was added to polymer solution and stirred on magnetic stirrer until homogenous solution was prepared. At last other ingredients like sodium starch glycolate, citric acid, sodium saccharine, vanillin were added. Prepared film solution was poured in petri plate and dried in room temperature for 24 hr. film was carefully removed after drying and cut into 2×2 cm.

Table 1: Composition of co-precipitate prepared by solvent evaporation method Preparation of orodispersible film by solvent casting method:

Formulation code	Daprodustat: beta cyclodextrin
F1	1:0.5
F2	1:1
F3	1:2
F4	1:3
F5	1:4

Calculation of the amount of drug for one cast film:

Internal diameter of Petri dish D = 6cm

Radius of Petri dish R = 3cm

Internal surface area of petri dish πr2= A

A= 28.26 (Dose of drug+ Beta cyclodextrin: 54.56 mg)

4cm^2 Contains = 54.56 mg

28.26 cm^{2}contains = 385.46 mg

Preparation of orodispersible film of optimized batches.

Composition of the orodispersible film is provided in table 2.

RESULT AND DISCUSSION

Evaluation of co-precipitate

Solubility Studies of Co- Precipitate

Solubility of all the formulation was determined and the formulation which showed better solubility was selected for further evaluation. Data is presented in table 3. In the solvent evaporation method SE3 showed highest solubility of 2.61±0.025 in water and 3.5577±0.035 phosphate buffer solution.

Evaluation of optimized batches of Orodispersible film

The orodispersible films exhibited consistent transparency across all formulations, with weight variation ranging from 51.23 mg to 78.56 mg, indicating uniformity within acceptable limits. Surface pH values remained within the neutral range (6.2–6.6), suggesting good compatibility with the buccal mucosa and minimal risk of irritation.

Table 2: Formulation Table of Optimized Batches of orodispersible Film

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Daprodustat (mg)	54.56	54.56	54.56	54.56	54.56	54.56	54.56	54.56	54.56
HPMCE5 (mg)	150	150	150	200	200	200	250	250	250
PEG400 (ml)	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
SSG (mg)	12	12	12	12	12	12	12	12	12
Citric acid(mg)	12	12	12	12	12	12	12	12	12
SS (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Vanillin (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water (ml)	10	10	10	10	10	10	10	10	10

Table 3: solubility studies of co-precipitate by solvent casting method

Formulation Code	Drug: Co-former	Ratio	Solubility (mg/ml) (n=3, ±SD) In water	Solubility (mg/ml) (n=3,±SD) In PBS 6.8	%Drug Content (n=3, ±SD)
SE1	Daprodustat: ß cyclodextrin	1:0.5	0.2006±0.049	1.8788±0.008	97.21 ± 0.54
SE2	Daprodustat: ß cyclodextrin	1:1	2.334±0.035	2.0019±0.030	98.73 ± 0.26
SE3	Daprodustat: ß cyclodextrin	1:2	2.61±0.025	3.5577±0.035	96.32 ± 0.77
SE4	Daprodustat: ß cyclodextrin	1:3	1.556±0.056	1.9988±0.032	98.19 ± 0.25
SE5	Daprodustat: ß cyclodextrin	1:4	1.333±0.07	1.444±0.083	97.11±0.54

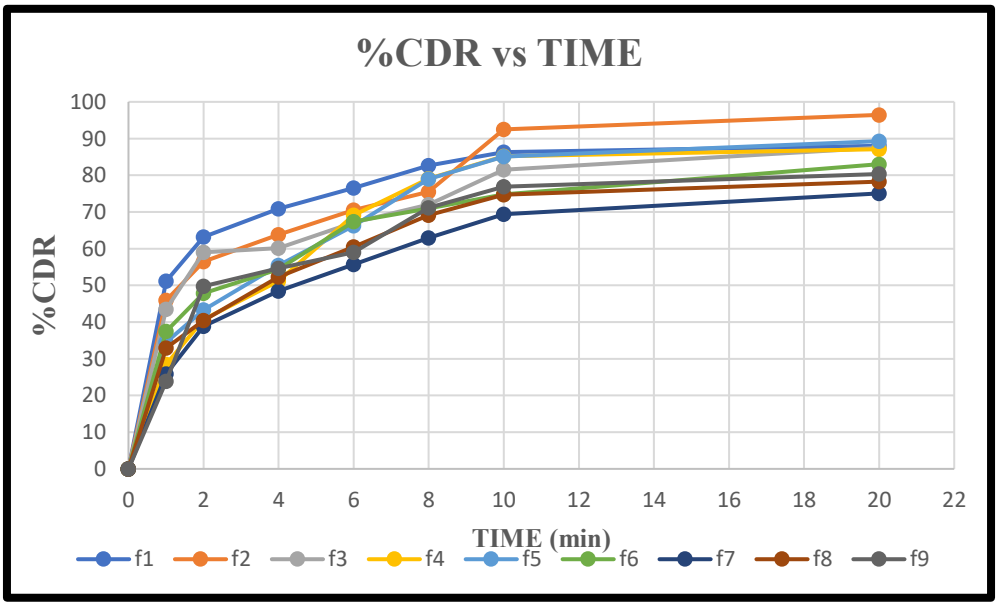
Table 4: Evaluation of optimized batches of Orodispersible film

Formulation Code	Thickness (mm) (n=3, ±SD)	Folding endurance (n=3, ±SD)	Tensile strength (Nmm^2) (n=3, ±SD)	Disintegration time (in sec) (n=3, ±SD)	% drug content (n=3, ±SD)	%Moisture Content (n=3, ±SD)
B1	0.103±0.005	156.6±16.9	4.2±0.22	33.66±3.21	87.36±0.6	3.2±0.04
B2	0.153±0.017	206.6±4.98	3.8±0.54	40.66±1.52	98.56±2.5	3.0±0.08
B3	0.187±0.005	63.33±2.86	1.6±0.07	42.61±0.52	90.10±0.3	2.9±0.11
B4	0.210±0.016	229.3±2.05	5.1±0.29	48.33±0.57	91.43±3.9	3.3±0.05
B5	0.223±0.021	272.3±2.49	4.3±0.18	52.33±1.52	90.24±2.6	3.6±0.07
B6	0.100±0.016	121.66±1.7	1.2±0.14	46.33±1.52	95.57±1.6	3.4±0.05
B7	0.157±0.017	314. ±9.74	5.6±0.29	57.33±1.52	97.21±0.3	3.4±0.01
B8	0.217±0.017	330.66±5.7	3.7±0.35	61.33±1.15	93.51±1.1	3.6±0.05
B9	0.123±0.012	113.3±5.73	1.9±0.35	49.33±0.57	92.28±1.9	3.4±0.07

All formulations exhibited acceptable physical properties. Tensile strength values mostly fell within the desired range (~2 N/mm^2), except B4, B5, and B7, which were slightly higher. Folding endurance was below 300 for most films, indicating good flexibility, with B8 slightly exceeding the limit. Overall, the films showed rapid disintegration, uniform drug content, and suitable mechanical strength for orodispersible use.

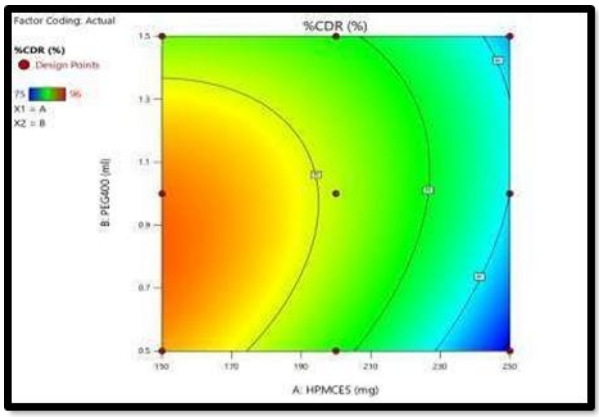
In-vitro drug release of optimized batches

The drug release increased steadily over time for all formulations. B1, B2, and B5 showed faster release, reaching over 85% by 10 minutes. All films released more than 75% of the drug by 20 minutes. This indicates effective and rapid drug delivery from the ODFs.

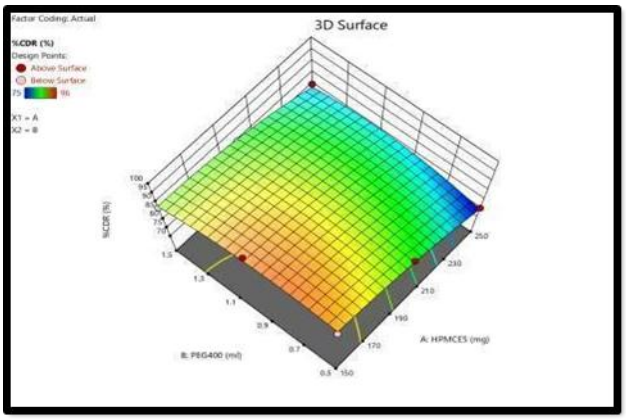


In-vitro drug release from B1–B9

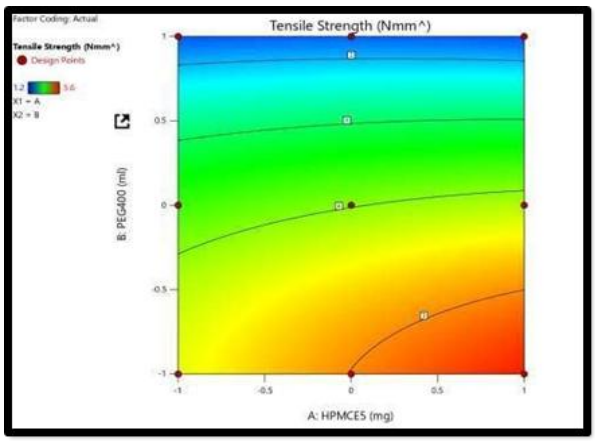
Analysis of Variance table ANOVA for Quadratic model Response



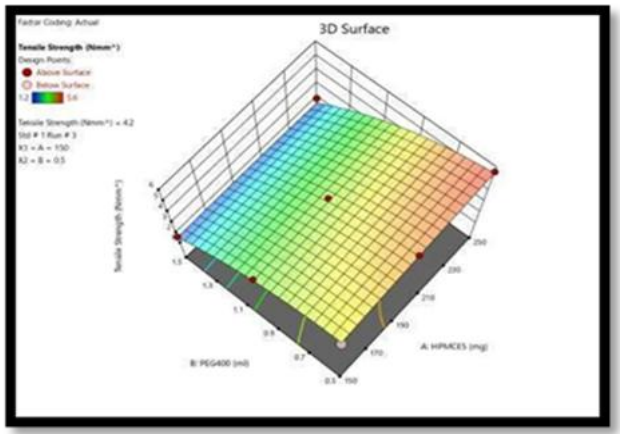
Contour plot showing the effect of HPMCE5 and PEG400 on response R1 (%CDR)



Response surface plot showing the effect of HPMCE5 and PEG400 on response R1 (%CDR)

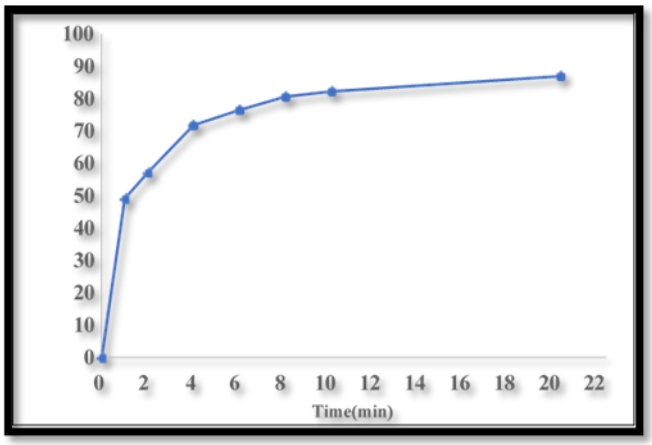


Contour plot showing the effect of HPMCE5 and PEG400 on response R2 (Tensile strength)



Response surface plot showing the effect of HPMCE5 and PEG400 on response R2 (Tensile strength)

Ex-vivo permeation studies of batch



Stability studies:

Table 5: Stability study evaluation

Parameters	0 Day	15 days	30 days
Thickness (mm)	0.153±0.01	0.152±0.11	0.152±0.02
Folding endurance	204.6±4.98	204±3.9	204±0.6
Tensile Strength (Nmm^2)	3.7±0.54	3.6±0.49	3.6±0.5
Disintegration time	38.66±1.52	38.12±1.4	38.01±0.3
% Drug content	98.56±2.5	97.56±2.5	97.45±0.4
% CDR	96.45	95.54	95.14

CONCLUSION

Orodispersible films were prepared by the solvent casting method using polymers such as HPMC E5, HPMC, and PVA at different concentrations, with PEG 400 and propylene glycol as plasticizers, along with other suitable excipients. Preliminary evaluation indicated that formulation F10 exhibited the highest drug release (79.61%) and satisfactory tensile strength (2.2 ± 0.54). Further optimization was carried out using a 3^2 factorial design. The developed ODF of Daprodustat provided immediate drug release, bypassed first-pass metabolism, reduced dosing frequency, and improved patient compliance.

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