

FORMULATION AND EVALUATION OF CLOPIDOGREL LOADED TRANSDERMAL PATCH USING DESIGN OF EXPERIMENTS

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Short title: Clopidogrel Transdermal Patch

ABSTRACT

The study investigated clopidogrel-loaded polymeric transdermal patches prepared with HPMC E15 and Eudragit RL100 and examined the effect of polymer levels on patch performance. Nine formulations were produced by solvent casting using the formulation components reported in the source thesis. HPMC E15 (250–350 mg) and Eudragit RL100 (100–200 mg) were varied according to the reported design-of-experiments matrix. The patches were examined for thickness, weight variation, folding endurance, moisture content, moisture uptake, tensile strength and 24-h in-vitro drug release using a Franz diffusion cell. Film thickness was 0.53–0.58 mm, folding endurance was 140–166 folds and tensile strength was 3.13–8.26 N/mm². The reported 24-h drug release was 86–97%; F6 had the highest reported value of 97%. The supplied thesis identifies a response-surface DOE approach using Design-Expert software, but the numerical ANOVA/model output was not available in the material reviewed. Therefore, no unverified statistical value or optimization claim has been added. The results support continued formulation optimization of clopidogrel transdermal patches using the original Design-Expert output and raw experimental records.

Keywords: clopidogrel; transdermal patch; HPMC E15; Eudragit RL100; solvent casting; design of experiments; drug release.

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INTRODUCTION

Transdermal delivery is intended to move a drug across the skin and, when systemic exposure is required, into the circulation. It can provide a controlled input profile and may reduce dependence on gastrointestinal absorption and hepatic first-pass metabolism. The main limitation is the low permeability of the stratum corneum, so polymer selection, film structure, drug properties and permeation-enhancing components are important during formulation development.^{1–4}

Clopidogrel is an antiplatelet prodrug used in the prevention of atherothrombotic events. The source thesis selected clopidogrel for experimental transdermal development and used a 10-mg drug load in a 2 × 2 cm patch. The work focused on polymeric matrix formation using HPMC E15 and Eudragit RL100, with additional formulation components including DMSO and PEG 400.

Response-surface design of experiments can evaluate formulation variables together and can reduce reliance on sequential one-factor-at-a-time trials. Such statistical approaches have been applied to transdermal films to study polymer levels and formulation responses.^{5–9}

MATERIALS AND METHODS

Materials

Clopidogrel, HPMC E15, Eudragit RL100, DMSO, PEG 400, polyvinyl alcohol, methanol and chloroform were the materials listed for the formulation work. The thesis identifies Research Lab Fine Chem as the source for the listed laboratory chemicals. Equipment included a UV spectrophotometer, FTIR instrument, magnetic stirrer, hot-air oven, Franz diffusion cell and related laboratory apparatus.

Preformulation and analytical method

Clopidogrel was assessed for appearance, odour, taste, physical nature, qualitative solubility and melting point. The reported melting point was 177°C, compared with a reference range of 176–178°C. Calibration solutions in methanol covered 0.2–1.2 µg/mL; the thesis reports $y = 0.1113x + 0.0032$ with $R^2 = 0.9973$. Drug content was described as an extraction in 1:1 methanol:chloroform followed by UV measurement at 338 nm against the solvent blank. FTIR was used to examine the drug and drug–polymer system.

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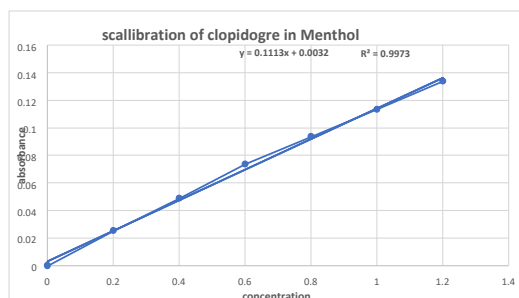


Figure 1. Standard calibration curve of clopidogrel in methanol.

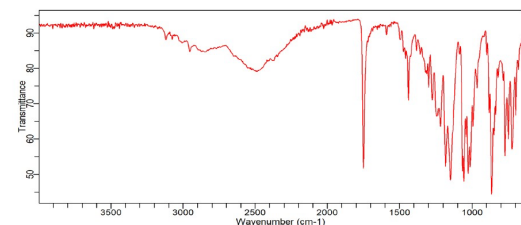


Figure 2. FTIR spectrum of clopidogrel.

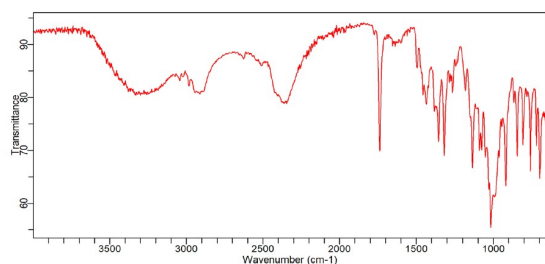


Figure 3. FTIR spectrum of the clopidogrel-loaded polymeric formulation.

Design of experiments

The thesis reports use of Design-Expert® version 13 for response-surface DOE. HPMC E15 (X1/A) and Eudragit RL100 (X2/B) were the two formulation factors. The thesis describes the design as a Box–Behnken response-surface design and lists percentage drug release (Y2) together with an optimization-related response identified as entrapment efficiency (Y1). Because the numerical Y1 results and complete model/ANOVA output were not available in the supplied results, they are not reproduced or inferred here. The exact design type should be confirmed from the original Design-Expert project before submission.

Table 1. Experimental formulation matrix and reported 24-h drug release.

Formulation	Clopidogrel (mg)	HPMC E15 (mg)	Eudragit RL100 (mg)	24-h release (%)
F1	10	250	100	91
F2	10	300	200	88

F3	10	250	150	96
F4	10	350	100	92
F5	10	300	100	86
F6	10	350	200	97
F7	10	250	200	93
F8	10	300	150	89
F9	10	350	150	90

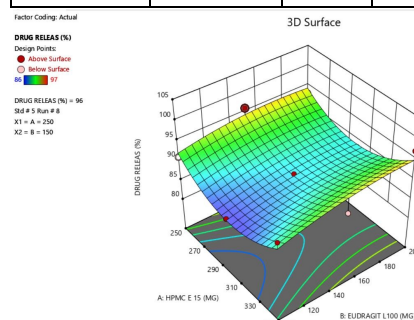


Figure 4. Three-dimensional response-surface plot showing the effect of HPMC E15 and Eudragit RL100 on percentage drug release.

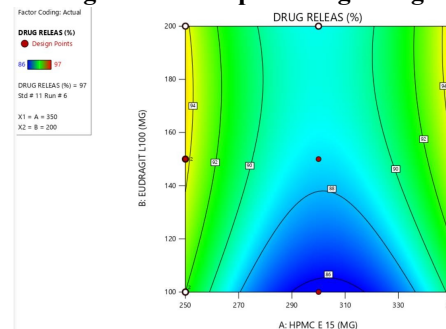


Figure 5. Design-Expert desirability/optimization plot or 3D response-surface output.

Preparation of transdermal patches

Each experimental patch measured 2 × 2 cm and was intended to contain 10 mg clopidogrel. The films were prepared by solvent casting. A polyvinyl alcohol backing membrane was prepared, while the casting mixture contained clopidogrel, HPMC E15, Eudragit RL100, DMSO, PEG 400, methanol and chloroform according to the formulation work. After mixing, the casting dispersion was transferred to a glass mould and allowed to form a film by solvent evaporation. The dried film was cut to the required patch size and stored as described in the source work.

Evaluation of patches

Thickness was measured at different locations using a digital vernier calliper. For weight variation, dried patch samples were weighed after drying at 60°C for 4 h. Folding endurance was determined by repeated folding at the same position until breakage. Moisture content was assessed after exposure to fused calcium

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chloride for 24 h, whereas moisture uptake was measured after exposure to saturated potassium chloride at approximately 84% relative humidity for 24 h. Drug content was described using three films per formulation, and percentage elongation at break was also determined. In-vitro release was performed with a Franz diffusion cell containing phosphate buffer pH 7.4 at $37 \pm 1^\circ\text{C}$. Three-millilitre samples were withdrawn at predetermined intervals and replaced with fresh medium; the experiment continued for 24 h.

Ethics statement. No human or animal experimentation was reported; the work comprised formulation development and in-vitro evaluation, so human/animal ethics approval was not applicable.

RESULTS AND DISCUSSION

Preformulation findings

Table 2. Preformulation and analytical findings.

Parameter	Reported observation
Appearance	White
Odour	Odourless
Taste	Tasteless
Physical nature	Amorphous powder
Solubility	Freely soluble in methanol and chloroform; sparingly soluble in methylene chloride; insoluble in ethyl ether and water
Melting point	177°C ; reference $176\text{--}178^\circ\text{C}$
Methanol calibration	$0.2\text{--}1.2\ \mu\text{g/mL}$; $y = 0.1113x + 0.0032$; $R^2 = 0.9973$

The reported preformulation observations provided the basis for selecting the solvent system and analytical procedure used for the patch study. The measured melting point was close to the cited reference range, while the methanolic calibration showed the reported linearity over the investigated concentration range.

Physical evaluation

Table 3. Physical and mechanical evaluation of clopidogrel transdermal patches.

Formulation	Thickness (mm)	Weight (mg)	Folding endurance	Moisture content (%)	Moisture uptake (%)	Tensile strength (N/mm ²)
F1	0.56 $\pm$ 0.03	53.67 $\pm$ 0.58	140 $\pm$ 1.31	5.23 $\pm$ 0.13	4.95 $\pm$ 0.17	8.26 $\pm$ 0.11
F2	0.53 $\pm$ 0.02	57.33 $\pm$ 0.58	151 $\pm$ 1.86	2.12 $\pm$ 0.21	2.65 $\pm$ 0.18	6.29 $\pm$ 0.23
F3	0.55 $\pm$ 0.03	64.67 $\pm$ 0.58	156 $\pm$ 1.12	2.67 $\pm$ 0.12	2.87 $\pm$ 0.23	5.33 $\pm$ 0.33
F4	0.55 $\pm$ 0.02	53.67 $\pm$ 0.58	150 $\pm$ 1.12	5.01 $\pm$ 0.11	4.82 $\pm$ 0.16	8.02 $\pm$ 0.11

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F5	0.58	63.67	145	4.76	3.89	6.3
	±	±	±	±	±	4 ±
	0.01	0.58	1.15	0.11	0.12	0.1
F6	0.55	52.00	161	4.12	3.34	3.1
	±	±	±	±	±	3 ±
	0.01	0.00	1.12	0.12	0.13	0.1
F7	0.55	57.67	158	4.44	3.12	5.7
	±	±	±	±	±	6 ±
	0.03	0.58	1.14	0.19	0.17	0.1
F8	0.55	51.00	159	4.01	2.51	6.5
	±	±	±	±	±	9 ±
	0.03	0.58	1.65	0.34	0.16	0.1
F9	0.56	55.00	166	3.39	3.27	4.6
	±	±	±	±	±	3 ±
	0.02	0.58	1.70	0.18	0.15	0.1

Across the nine formulations, thickness remained within 0.53–0.58 mm. Folding endurance varied from 140 to 166 folds, while tensile strength ranged from 3.13 to 8.26 N/mm². Moisture content and moisture uptake were 2.12–5.23% and 2.51–4.95%, respectively. The variation across batches indicates that polymer composition affected the mechanical and moisture-related properties of the films.

Figure 6. Photograph of the prepared clopidogrel transdermal patch.

In-vitro drug release

Table 4. Reported cumulative drug release after 24 h.

Formulation	24-h cumulative drug release (%)
F1	91
F2	88
F3	96
F4	92
F5	86
F6	97
F7	93
F8	89
F9	90

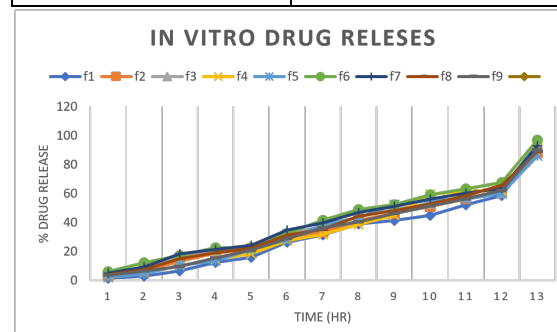


Figure 7. Cumulative in-vitro drug release profile of F1–F9 over 24 h.

The reported 24-h release ranged from 86% to 97%. F6 had the highest reported value (97%), followed by F3 (96%) and F7 (93%); F5 had the lowest value (86%). These differences are consistent with an influence of the HPMC E15/Eudragit RL100 composition on release behaviour, although the individual factor effects and interaction cannot be quantified reliably without the original Design-Expert model output. The source thesis contains an apparent transcription error in the F2 value at 3 h (reported as “13023”); this value must be checked against the laboratory/Excel record before Figure 7 is finalized.^{10–14}

DOE interpretation

The experimental matrix demonstrates a formulation space spanning three HPMC E15 levels and three Eudragit RL100 levels. Response-surface methods have been used in transdermal formulation studies to examine polymer combinations and identify promising formulation regions.^{8,9} The 24-h release values show substantial variation across the nine runs. However, the numerical ANOVA table,

regression equation, p-values, model adequacy statistics and confirmed desirability solution were not available in the supplied material. Consequently, F6 is reported only as the batch with the highest recorded 24-h release, not as a statistically validated optimum. The original Design-Expert project should be used to establish the final optimized formulation and to populate Figures 4–5.

CONCLUSION

Clopidogrel-loaded transdermal films containing HPMC E15 and Eudragit RL100 were prepared by solvent casting and evaluated using physical, mechanical and in-vitro release tests. The reported film thickness was 0.53–0.58 mm, folding endurance was 140–166 folds and tensile strength was 3.13–8.26 N/mm². Cumulative drug release after 24 h was 86–97%, with F6 giving the highest reported value of 97%. These findings establish the experimental formulation range but do not by themselves provide a statistically confirmed optimum. Final DOE claims should therefore be based on the original Design-Expert ANOVA, model diagnostics and desirability output.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

No external funding was reported for this study.

ETHICAL APPROVAL

No human or animal experimentation was reported; the work comprised formulation development and in-vitro evaluation. Therefore, human/animal ethics approval was not applicable.

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