Ind. J. Pharm. Edu. Res., 2024; 58(2s):s444-s452.
https://www.ijper.org

Original Article

Quality by Design (QbD) Aided Formulation Optimization of Amlodipine Besylate Oral Thin Film

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ABSTRACT

Background: Oral Thin Film (OTF) is an emerging approach for oral drug delivery but still there exists a scarcity of evidence for formulation optimization techniques. Herein, we aim to develop OTFs optimized by the QbD approach. **Materials and Methods:** OTFs were prepared by solvent casting method using Amlodipine as an active ingredient and excipients such as Pectin, Aspartame, Tween 80, and Glycerine. The developed formulation was optimized using QbD software Design Expert version 8.0.4, USA. The independent variables of the experiment were selected as A-pectin, B-Tween-80, and C-glycerine, and the dependent variables were R1-tensile strength (kg/cm^2), R2-permeation rate (µg/cm^2/hr), R3-disintegration time (in a sec). Finally, the software suggested optimized formulation based on a desirability value closer to 1. **Results:** The optimized oral films were comparatively evaluated and characterized by various techniques. The drug release was found to be ~96% at 10 min for OTFs and ~94% at 20 min for oral fast-dissolving tablets. The amlodipine was scanned in the UV range of 200 to 400 nm and the λ_{max} was observed to be at 240±2 in a Phosphate of pH 6.8. **Conclusion:** All results are found satisfactory and well within the acceptance range. This ensures that similar formulations can be optimized by using this technique in the future.

Keywords: Oral thin film (OTFs), Solvent casting method, Quality by design (QbD), Optimization, Drug release.

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Received: 26-07-2023;
Revised: 14-11-2023;
Accepted: 20-01-2024.

INTRODUCTION

Owing to the presence of vascularization, oral mucosa can directly absorb drugs which can eventually set foot in systemic circulation bypassing the first-pass metabolism. Development strategy of new products with molecules with more susceptibility to endure first-pass metabolism can explore this privilege of vascularized oral mucosa as a lucrative site for drug delivery.[1] This ensures the advent of a drug delivery system colloquially known as an Oral Thin Film (OTF) or soluble film as per the FDA or orodispersible film as per the European Medicines Agency (EMA) which has a fascinating feature of fast dissolution (within a minute or so) in the oral cavity. Commonly, these OTFs, having a width of 50-150 µm and the size of a postage stamp, quickly start dissolving once it touches the saliva followed by prompt absorption and immediate bioavailability of the drugs in the systemic circulation.[2] Other appealing traits of OTFs are-it's needless to use water for their delivery and ease of transport.[3,4]

To enhance and upgrade the standard of pharmaceutical products, a broad, effective, structured, and comprehensive design tool with less risk has been implemented, which is known as Quality by Design (QbD).[5] Covering the parts or entire process ranging from ideation, and R&D to large-scale manufacturing of pharmaceutical product development, QbD can be efficiently executed.[6] Throughout the optimization technique, the R&D cost can be minimized, the gap between scientific ideation and industrial production can be bridged up, and the knowledge transfer process to further introduction of novel drugs/delivery systems to the market can be facilitated as well.[7,6] According to ICH Q8, QbD is defined as "a systematic approach towards development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".[8] In essence, QbD is a powerful technique to optimize any kind of pharmaceutical formulation.[9,10] Yet, there exists a scarcity of evidence for OTF optimization techniques utilizing QbD.[11]

DOI: 10.5530/ijper.58.2s.48

To this end, we applied the QbD approach for the development of OTFs to deliver amlodipine which is a protracted dihydropyridine calcium antagonist and is one of the most often prescribed antihypertensive drugs globally.[10] QbD software Design expert version 8.0.4, USA was used for design optimization, and various independent and dependent variables were selected combination of which yielded the desirable formulation. The OTF formulation was developed with active and inactive excipients. Pectin was selected as a biodegradable film-forming agent along with low contents of Polyethylene Oxide 2000 (PEO2000) as the carrier polymer to produce electro-spun fibers, aspartame was used as sweetener, Tween 80 was used as a surfactant or permeation enhancer and glycerine was used to balance tensile strength.[12,13] The developed OTF formulation was characterized by various analytical methods to ensure that the proposed formulation is therapeutically effective and safe with quality attributes. Drug content, disintegration time, and tensile strength were measured. Drug release study and drug permeation study were performed *in vitro*. Taken together, the findings of the study can be explored further for QbD optimization and the development of novel OTFs with various drugs in the future.[14]

MATERIALS AND METHODS

Materials

Amlodipine besylate was procured from Yarrow Chem Pvt. Ltd., (Mumbai), tween-80, aspartame, glycerol, and pectin (Product no.S419095) were procured from Sigma-Aldrich (USA). Subsequently, methanol, acetonitrile, sodium dihydrogen phosphate, potassium dihydrogen phosphate, HCl, and citric acid, were procured from Merck Limited (USA). All the chemical and reagent used in this research work was of highly pure and chromatographic grade. Glassware and instrument facilities were used in-house (Esperer Onco Nutrition Pvt. Ltd.,).

Methods

Fabrication of Oral Thin Film (OTFs)

OTFs were fabricated by a solvent-casting technique using a drug and various excipients i.e. HPMC 50 LV, Pectin, Glycerol, fructose, aspartame, citric acid, tween-80, water, ethanol, and coloring agent.[15] Initially, the amount of excipient and drug were taken based on Table 1 polymers were taken in 50 ml beaker with previously added 10 ml water, plasticizer was added in defined amount and kept under magnetic stirring for 1 hour until the clear solution was formed and the beaker was kept aside for 20 to 30 min at room temperature. In another beaker, citric acid and the drug were dissolved in ethanol under a magnetic stirrer. In the former beaker, the required quantity of surfactant (tween 80) and sweetening agent (fructose and aspartame) were added and continued for 30 min. Finally, both the solutions were mixed, and coloring and flavoring agents were added q.s. and continued stirring for 2 hr. The resulting solution was kept for 30 min to remove entrapped air bubbles and finally poured into petri plates and kept at room temperature. Further, the Petri plate was kept in the oven at 55°C for 10 min. The dried film was cut in a 2 X 2 cm^2 area and characterized as the quality control parameter.[8,16] Same methodology was carried out for placebo preparation.

OTF Design by BBD

Here, the Box-Behnken Design (BBD) was used for a surface response.[17] Previously, the upper and lower limit of polymers was optimized based on Table 1, and the 3 response factor model was used to design the experiment. The proposed formulations were optimized on a three-factor three-level using Box–Behnken factorial design.[17] The independent variables were selected as A-pectin, B-Tween-80, and C-glycerine, and the dependent variables were R1-disintegration time (in a sec) R2-tensile strength (kg/cm^2), R3-permeation rate (µg/cm^2/hr). Moreover, the independent variable was selected in the lower and upper range with 3 composite points and based factors adequate 13 number of trials were carried out for optimization.[18]

Characterization of OTFs

Spectroscopic method

A validated UV-Spectrophotometric method was used for the quantitation of amlodipine from OTFs.[19] Initially, calibration plots were generated with a sample in pH buffer 6.8 within the scan range 200 to 400 nm and found correlation coefficient r^2 0. 9937 and λ_{max} 240 nm. This method was suitable to quantitate amlodipine from OTFs. UV-spectrometry was used for the evaluation of quality control parameters like *in vitro* drug release studies, drug content, and permeability studies.[10]

Calibration Plot

Prepared 1000 µg/mL stock solution by weight of 100 mg amlodipine and was transferred into 100 mL of a volumetric flask containing 50 mL of phosphate buffer, pH 6.8. Thereafter, sonicate the resulting solution till particles are dissolved and made up to volume with the same buffer. Further, seven different dilutions were made from the initial stock solution (1000 µg/mL) i.e., 2, 4, 8, 16, 32, 64, and 128 µg/mL for the establishment of calibration plot. The maximum absorbance was recorded at λ_{max} 240 nm. The final linearity graph was plotted concentration µg/mL vs absorbance. Eventually, r^2 and slop and Intercept were calculated.

Drug Content

Firstly, cut 1 cm^2 of OTF from the center part of the casted films and transfer them into a 10 mL volumetric flask containing 5 mL of PBS buffer. Followed by sonicating the solution till particles were dissolved and made up to the volume with the same buffer. Further, the resulting solution was filtered through a 0.45 µm syringe PVD filter and made a suitable dilution. Finally, the solution was tested by UV spectrophotometer at λ_{max} 240 nm.

$$A = abc\text{------}1$$

Where A: absorbance, a: molar absorptivity, b: thickness of path length, C: concentration.

Estimation of Disintegration Time

The disintegration test for amlodipine oral thin films is an important evaluation to ensure that the film dissolves or disintegrates in the mouth within a specified time frame. This is critical for assessing the performance and efficacy of oral thin films. In the present study, we designed an OTF formulation for rapid drug delivery and ease of administration in systemic circulation. The developed OTF formulations were tested on USP disintegration apparatus, equipped with appropriate baskets and/or tubes. Thereafter, we set all physiological conditions to mimic the oral cavity, including temperature, pH, and buffer media; Placed a single oral thin film in each tube into the disintegration apparatus. Further, Start the disintegration apparatus and allow the films to disintegrate or dissolve under the specified conditions. The time was recorded in seconds. The disintegration time limit below 59 seconds or less is considered to be worthwhile.

Tensile Strength

Texture Pro CT V1.3 Build 15, Brookfield, a texture analyzer machine containing two load cells grasps-upper and lower, was used to determine the tensile strength of the OTFs. Once OTFs were placed between the cell loads, the power was gradually applied until the films fell into pieces. The dial reading indicated the amount of tension needed to fragment the OTFs. All measurements were performed in triplicates (n=3).

In vitro drug permeation study

In order to measure *in vitro* drug permeation from the OTF, Franz diffusion cell was used which comprises the donor and receptor compartments which were filled up with 5 mL and 45 mL PBS with 0.1% tween 80 (pH 6.8) respectively. OTFs and cellophane membranes (12,000-18,000 mol. wt. cut-off) having an area of 2 X 2 cm^2 were fixed on a diffusion cell placed between the two chambers.[20,21] Temperature was maintained at 37±0.5°C and the speed 100±5 RPM on a magnetic stirrer with a hot plate (Ika, Germany). Aliquots of 1 mL were collected at 1 hr interval and drug permeation through a membrane was measured by UV/vis spectrophotometry. The experiment was conducted in triplicates (n=3).

In vitro Drug Release Study

USP-V dissolution apparatus type-V was used to evaluate *in vitro* drug release of OTFs, which contained 500 mL of phosphate buffer (pH 6.8) dissolution medium maintained at 37°C±0.5°C with a 50 rpm rotation speed. 2 X 2 cm^2 films were poured inside dissolution basket along with a cover-up disc. Aliquots of 5 mL were collected from each vessel at pre-determined time intervals, filtered, and analyzed by using a spectrophotometer (single beam microprocessor-UV, model no. YIS 295) at 240 nm. Each time, the volume in the vessel was replenished with fresh buffer (5 mL) to maintain the sink condition.

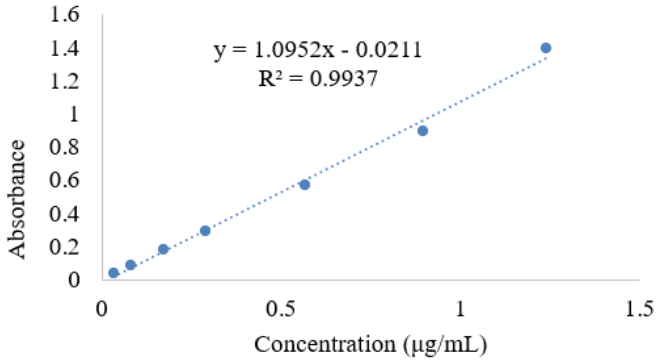

Figure 1: Calibration plot of amlodipine in phosphate buffer pH 6.8, λ_{max} 240 nm.

Table 1: Preliminary polymers and excipients have been optimized with various concentration ratios up to F9.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	10	10	10	10	10	10	10	10	10
HPMC50LV (mg)	150	250	275	300	-	-	-	-	-
Pectin (mg)	-	-	-	-	150	200	250	300	350
Citric acid (mg)	20	20	20	20	20	20	20	20	20
Glycerol (mg)	150	175	200	225	225	275	225	175	125
Tween-80 (%)	0.2	0.4	0.8	1.6	0.5	1	1.5	2	2.5
Aspartame (mg)	-	-	-	-	1	1	1	1	1
Fructose (mg)	60	60	60	60	-	-	-	-	-
Ethanol (Q.S mL)	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Water (Q.S mL)	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Coloring agent (mg)	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Flavoring agent (µL)	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

RESULTS

Calibration plot

We have scanned the amlodipine between the 200 to 400 nm range and the maximum absorbance was found at 240±3 nm in phosphate buffer (pH 6.8). Subsequently, we established the calibration plot in the same buffer with r^2=0.993 and y=1.0952x-0.0211 as depicted in Figure 1 and Figure S1.

Formulation development

We optimized the amount of various excipients by making nine formulations (F1 to F9) and identified the suitable excipients that played a potential role in OTF formulation development. Moreover, we have also optimized the concentration of these excipients at maximum and minimum levels. The detailed studies are summarized in Table 1 and Figure S2.

Formulation optimization

We applied the QbD surface optimization model (Box Behnken model) with three center points; the proposed model suggested 13 runs with three response factors. Subsequently, we developed 13 formulations and evaluated all three response factors. The data are reported in Table 2. Eventually, all the results were placed in a table and used quadratic equation surface optimization. Our designed model showed R^2 0.995±0.025, a summary of fit suggested by the software was a quadratic equation, while models are significant (*p* value 0.0003) and the lack of fit is not significant (*p* value 0.0682), as reported in ANOVA Table 3 and Figure 2. Subsequently, DOE software created a three-dimensional model graph for disintegration time in (sec), tensile strength (kg/cm^2), and permeation rat (mg/cm^2/hr) which has given a rough idea about the optimistic concentration of polymers or/and excipients. The 3D model graphs are depicted in Figure 3 (A,B and C) respectively. Finally, we have selected one formulation based on a desirability value closer to 1 which is depicted in Figure S3 and S4, and similarly, the parato graph represents an overall optimistic view of this (BBD model) as depicted in Figure S5.

Drug content

Drug content was estimated to ensure uniform dispersion of the drug throughout the film. It was evaluated by UV analysis at 240 λ_{max}, and content was found in oral thin films to be 97.3±2% and solid oral formulation at 98.6±2% respectively. Comparatively, both formulations showed good results and passed the drug content as per Indian Pharmacopeia (IP).

Disintegration time

It is a time after which film collapses when brought into contact with water. The disintegrate time for the final optimized formulation of OTF was shown to be ~ 27±2 sec, while a solid oral marketed tablet took more time 57±sec to disintegrate. This shows that our formulation has shown a slightly better disintegration time compared to a solid oral fast-dissolving tablet.

Tensile strength

The measurement of tensile strength for the optimized OTF formulation was carried out using a Texture analyzer testing machine (Texture Pro CT V1.3 Build 15, Brookfield). The OTF film was fixed in a texture analyzer applied mechanical force was applied between two directions and tension (kg/cm^2) was indicated. The tensile strength of the OTF formulation was recorded to be 0.95 kg/cm^2, beyond which it became brittle.

Table 2: Experimental Run Table (*n*=13, numbers of center point=3), Where: A: Pectin, B: Tween 80, C: Glycerol and R1-disintegration time (in sec) R2-tensile strength (kg/cm^2), R3-permeation rate (µg/cm^2/hr).

Std.	Run	A	B	C	R1	R2	R3
4	F1	300	250	0.95	75	2	0.587
9	F2	50	-150	-0.1	45	1	0.123
12	F3	50	250	2	67	1.5	0.63
11	F4	50	-150	2	40	1	0.678
7	F5	-200	50	2	54	1.6	0.667
14	F6	50	50	0.95	28	0.2	0.398
2	F7	300	-150	0.95	66	1.8	0.374
8	F8	300	50	2	72	1.5	0.656
6	F9	300	50	-0.1	59	1.2	0.129
3	F10	-200	250	0.95	57	1.8	0.367
1	F11	-200	-150	0.95	39	1.3	0.42
5	F12	-200	50	-0.1	46	1	0.133
10	F13	50	250	-0.1	35	1	0.145
15	F14	50	50	0.95	30	0.2	0.414
13	F15	50	50	0.95	29	0.3	0.418

Table 3: ANOVA Analysis of variance.

Source	*F*-Value	*p*-Value	R^2
R1 Disintegration time in second			
Model	45.52022	0.0003	Significant**
A-Pectin	82.98851	0.0003	0.987943
B-Glycerol	27.81609	0.0033	
C-Tween 80	33.10345	0.0022	
AB	2.327586	0.1876	
AC	0.718391	0.4354	
BC	39.33908	0.0015	
A^2	180.5371	<0.0001	
B^2	39.31698	0.0015	
C^2	28.01724	0.0032	
Lack of fit	13.83333	0.0682	Not significant
R2 Tensile Strength (kg/cm^2)			
Model	46.42633	0.0003	Significant**
A-Pectin	4.080686	0.0994	0.988175
B-Glycerol	9.361124	0.0281	
C-Tween 80	14.4153	0.0127	
AB	1.250232	0.3143	
AC	1.383969	0.2924	
BC	3.801144	0.1087	
A^2	234.5661	<0.0001	
B^2	151.5882	<0.0001	
C^2	47.24074	0.0010	
Lack of fit	0.977575	0.5416	Not significant
Permeability (mg/cm^2 /hr)			
Model	58.72933	0.0002	Significant**
A-Pectin	1.916944	0.2248	0.990629
B-Glycerol	1.957751	0.2206	
C-Tween 80	492.753	< 0.0001	
AB	11.94249	0.0181	
AC	0.000471	0.9835	
BC	1.100285	0.3422	
A^2	0.372187	0.5685	
B^2	0.334875	0.5879	
C^2	17.32199	0.0088	
Lack of fit	19.00749	0.0504	Not significant

Permeation study

Permeation study deciphers the rate and extent of permeability of the drug from the dosage form. It was carried out using a Franz cell diffusion apparatus where OTF formulation was placed in a donor compartment in a sandwich-like structure with an acceptor compartment that was filled with phosphate buffer media (pH 6.8) and the instrument was run for 60 min with a predefined time interval. Analysis of the sample was done by UV-Spectrophotometer at λ_{max} 240 nm and the permeation rate was found to be 0.975 mg/cm^2/hr (Figure 4).

In vitro drug release

Release kinetics is important to derive the time rate of drug release pattern from the dosage form. After 10 min, the drug release

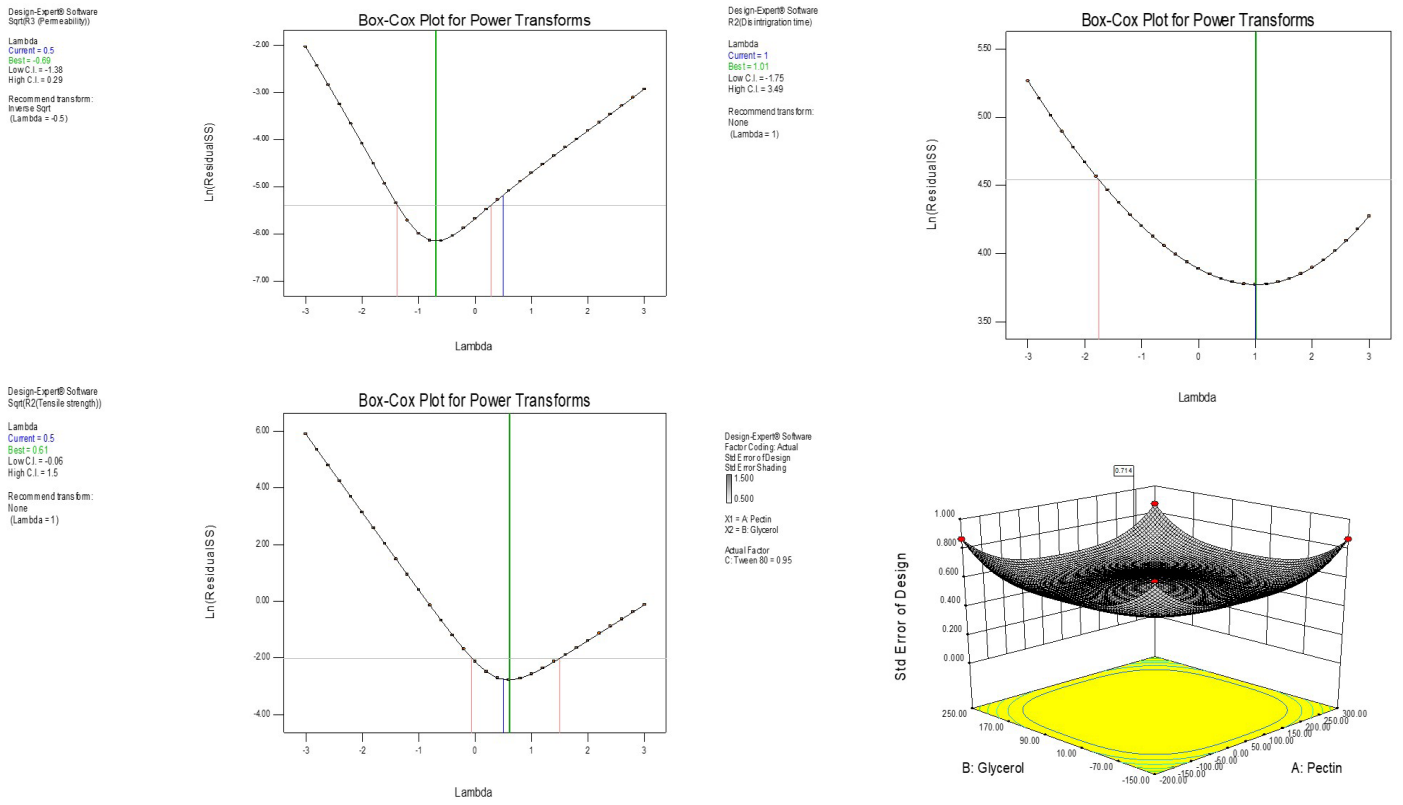

Figure 2: [A] Box-Cox plot for power transformation for R3 response factor with optimized recommended model square root, [B] Box-Cox plot for power transformation for R2 response factor and no recommendation by software similar for, [C] R3 response factor and finally, [D] Polynomial model 3D model graph with fallowed order quadratic order.

was observed to be ~96±2% for oral thin films and ~65±1.5% for mouth dissolving tablets. After 20 min, we found that both formulations showed similar drug release profiles 86% and 95% respectively. The experimental data are summarized in Figure 5, where the blue line represents OTF formulation, and the orange line represents mouth-dissolving solid oral tablet formulations. So, a comparatively better drug release profile was observed for OTF formulation than that of fast-dissolving oral tablets.

DISCUSSION

Currently, Amlodipine besylate is available in the market in solid oral formulations like a tablet, capsules, and liquid dosage forms such as oral suspension (Brand Name: KATERZIA). A few pharmaceutical companies such as Pfizer, Dr. Reddy laboratories, Lupin Limited, and Aurobindo Pharma Limited are global leaders in manufacturing this medicine. We envisage that our proposed OTF formulation will add value and contribute significantly to the field of oral mucoadhesive drug delivery, which will improve the oral bioavailability of amlodipine besylate bypassing the first-pass metabolism. Preliminary investigations of our proposed formulation prompted us to undertake a clinical evaluation of the dosage form for hypertension.

Recently USFDA approved an OTF of "Suboxone" sublingual film, which may increase access to treatment for opioid dependence. FDA has taken a new initiative to ensure the advanced development and treatment of opioid patients. However, there are limitations still existing for OTF formulation such as disintegration, taste masking, and poor drug release. Herein, we tried to address these issues by developing a new OTF formulation using the QbD approach. There are various design models available for optimizing the formulation i.e., Box-Behnken Design (BBD), central-composite design, factorial design, D-optimal design, and mixture design. Here, a Box-Behnken design was employed for the optimization of OTF and experimental data revealed that our proposed model is significant (0.003) and lacks fit 0.220±0.227.[23,24] ANOVA results have elaborately been portrayed in Table 3. Subsequently, OTF was prepared by using the solvent-casting method without utilizing any sophisticated instrument in the laboratory.[8] Moreover, this approach is suitable for developing a new product for pediatric and geriatric populations minimizing patient compliance while at the same time improving patient acceptability, safety, and efficacy.

Our present quality attribute is more relevant than the conventional optimization process, throughout this technique we minimized tedious trials at the research and development (R&D)

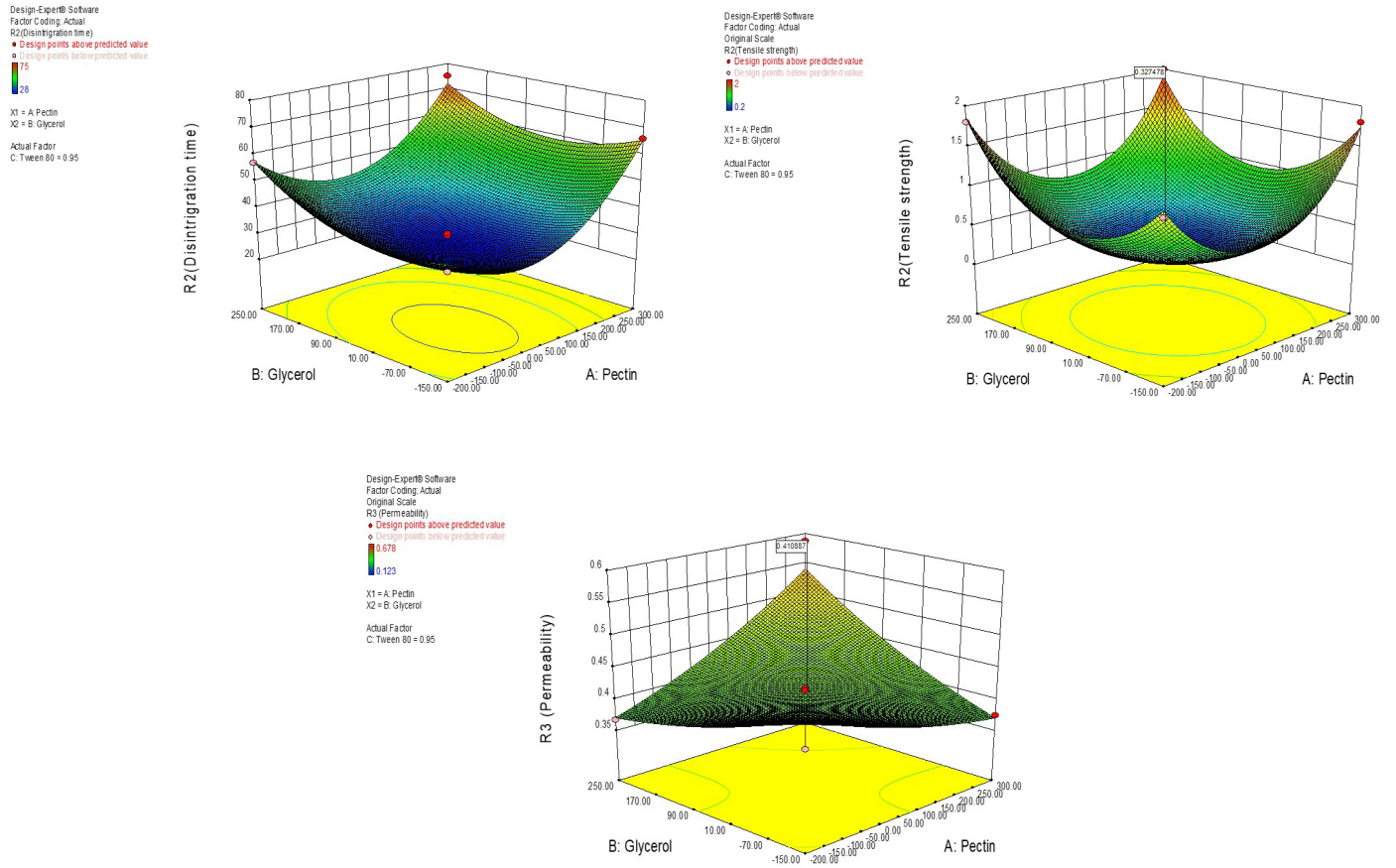

Figure 3: [A] 3D Surface model graph of Disintegration time in sec, [B] Tensile strength and [C] permeation rat (mg/cm²/hr).

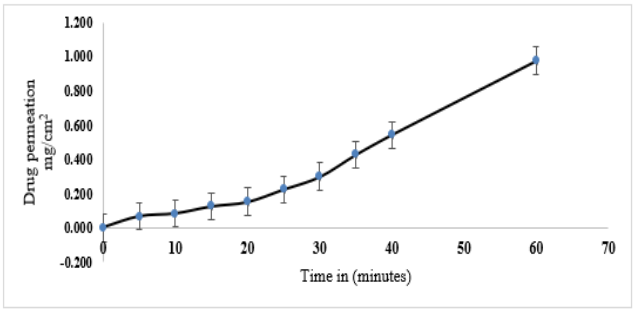

Figure 4: The depicted graph shows the drug permeation study of amlodipine and the maximum permeation rat was shown 0.975 mg/cm²/hr.

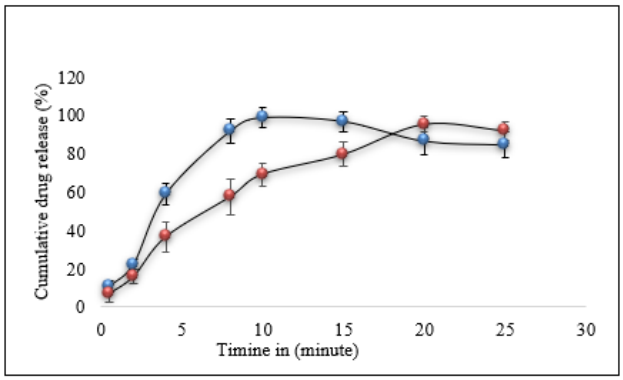

Figure 5: The drug release profile of amlodipine while the blue solid line represents OTFs and similarly orange solid line Mouth dissolving tablet MDT.

stage and decreased the amount of material used in R&D which is beneficial for cost-cutting and lesser time consumption. We successfully established a calibration plot of amlodipine in PBS buffer (pH 6.8) with maximum absorbance of amlodipine at 238 and got r^2=0.993, as shown in Figure 1, which matches the previous reports.[22,25,26] Also, our findings revealed that oral thin films were showing a faster drug-release rate compared to mouth-dissolving tablets. All the experimental data are reproduced N=3 and applied in standard deviation (±SD). Moreover, results demonstrated that OTFs have better disintegration time compared to a solid oral formulation. Overall, our experimental data is congruous with the fact that QbD can be utilized for the design of OTFs which can be a better option for mucoadhesive drug delivery.

CONCLUSION

In conclusion, our findings revealed that the QbD technique can be implemented towards developing OTF with less effort. The proposed formulation can minimize the optimization

process of OTF product development by reducing tiresome R&D trials leading to an overall improvement of quality attributes. Compared to other solid orals, amlodipine OTFs demonstrated better disintegration time and drug release. More in-depth patient trials are required to prove its superiority in terms of oral bioavailability.

ACKNOWLEDGEMENT

The authors acknowledge Dr. Veerma Ram (Director), and Dr. Vikas Anand Saharan (Prof. and Head) School of Pharmaceutical Sciences, Sardar Bhagwan Singh University for providing us with ideation of the proposed research work. We would also acknowledge Dr. Kumar Pranav Narayan (Professor), Department of Biological Sciences, Birla Institute of Technology and Sciences-Pilani, Hyderabad Campus for technical support and guidance. The authors also would like to acknowledge whoever directly and indirectly helped us to accomplish this research work, Dr. Priyanka Maurya-Plagiarism check (Professor, BBDNIIT), and Dr. Raktim Chattopadhyay-Chemical and reagents (Managing Director-Esperer Onco Nutrition Private Limited).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

mg: Milligram; **mL:** Milliliter; **µL:** Microliter; **µm:** Micrometer; **ACN:** Acetonitrile; **HPLC:** High-Performance Liquid Chromatography; **BCS:** Biopharmaceutical Classification System; **API:** Active Pharmaceutical Ingredient; **OTF:** Oral Thin Film; **QbD:** Quality by design; **EMA:** European Medicines Agency; **ICH:** International Council for Harmonization; **BBD:** Box-Behnken Design; **IP:** Indian Pharmacopeia; **FDA:** Food and Drug Administration; **USFDA:** United States Food and Drug Administration.

SUMMARY

In summary, we implemented the QbD approach for the development of OTFs to deliver amlodipine which is a protracted dihydropyridine calcium channel blocker and is one of the most often prescribed antihypertensive drugs globally. QbD Software Design expert version 8.0.4, USA was used for design optimization, and various independent and dependent variables were selected combination of which yielded the desirable OTF formulation comprising active and inactive excipients. Our findings revealed that the QbD technique can be utilized towards developing OTF with less effort. The developed OTF formulation was optimized by the QbD approach and offered better formulation compared to the conventional technique with respect to quality. Further, characterized by various analytical methods to ensure that the proposed formulation shows promising results. Compared to other solid orals, amlodipine OTFs demonstrated better disintegration time and drug release. More in-depth patient trials are required to prove its superiority in terms of oral bioavailability. Taken together, the findings of the study can be explored further for QbD optimization and the development of novel OTFs with various drugs in the future.[27,28]

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Cite this article: Kumar A, Kumar M, Singh R, Upadhyay P, Mukherjee A. Quality by Design (QbD) Aided Formulation Optimization of Amlodipine Besylate Oral Thin Film. Indian J of Pharmaceutical Education and Research. 2024;58(2s):s444-s452.