Research Article

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Industry-Patient-Friendly Tadalafil Oral Spray: Statistical Development, Functionality and *In-Vivo* Taste Assessment

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ABSTRACT

The current work aimed to design a new patient-friendly Tadalafil (TDL) oral spray for management of erectile dysfunction employing concept of advanced data mining and analytical tools. An inclusion complex of TDL: Dexolve®, was formulated and characterized for its physicochemical properties. Phase solubility study suggested a 1:1 ratio of TDL: Dexolve® showed higher solubility. FTIR, DSC, and XRD studies confirmed the partial alteration of crystalline to amorphous. The complex assessed *in-vivo* for taste masking inculcating the Brief Access Taste Aversion (BATA) model, indicated the taste masking of TDL. The complex was incorporated into spray formulation using water: ethanol, Vitamin D and HPMC E5. MLRA and ANOVA depicted the crucial correlation between amount of ethanol and HPMC E5 with spray pattern and % TDL release. The results of characterization suggested that it covered the maximum area of the oral cavity, indicated uniform distribution and more absorption. The design batches were evaluated for varied oral spray-related parameters and stability studies. The formulation was found stable and released TDL immediately. Dexolve® was found to be a promising multifunctional excipient. The oral spray prepared was environmentally friendly as it is propellant-free. The newer stable and immediate-acting spray improves release of TDL and is patient-friendly.

Keywords: Tadalafil, BATA model, Oral spray, Vitamin D, Dexolve®

1. Introduction

Erectile dysfunction (ED) could be explained by employing the "inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1]." Around 100 million men have erectile dysfunction worldwide [2]. The prevalence of ED was 52% worldwide and will increase shortly. The category with the utmost occurrence was moderate to minimal to complete ED at 25%, 17%, and 10%, respectively [3],[4]. Three treatments have recently been available to manage ED [3],[6]. Oral phosphodiesterase type 5 (PDE-5) inhibitors are preferred because of industry and patient-friendly treatment [7]–[10]. Sildenafil and TDL are widely used PDE-5 inhibitors [11]. Due to a longer half-life (36h) and < 0.1% vision deviancy, TDL was considered first-line treatment.

TDL and many more drugs have numerous limitations, like less bioavailability due to high first-pass metabolism, poor aqueous solubility, slow onset of action, bitter taste, and degradation in gastrointestinal tract [12],[13]. A novel oral TDL spray can avoid the first-pass metabolism and also the degradation of the drug into the unfavorable GIT conditions. In addition, due to busy lifestyles, people expect lifestyles and immediate action of the medicine with better patient compliance. Nowadays, many attempts are made to improve the onset of action with fewer side effects. The novel oral spray of TDL was attempted to locate this issue. TDL oral spray formulation was targeted to the oral cavity for better absorption, immediate action and avoidance of first-pass metabolism. Use of Vitamin D with TDL to improvise the condition of ED was observed. Vitamin D deficiency has the major role in ED symptoms. The use of Vitamin D with TDL will improve the therapeutics efficiency. Pharmaceutical industries are continuously trying to use FDA-approved excipients, which have multiple roles in the formulation. Using such excipients decreases the overall production cost, provides better control of the product's life cycle management, and allows easy scale-up and validation of the process. Dexolve® was explored to resolve the problems related to the drug's aqueous solubility, stability and taste [14]. Dexolve® has the unique characteristics as a multifunctional excipient. It is chemically a sulfobutyl ether beta-cyclodextrin (SBE-β-CD) which engulf the bitter and hydrophobic drug inside its cage like structure by forming non-covalent complex. Due to the formation of complex, it improves the solubility and bioavailability. It is much more promising agent compared to other cyclodextrin derivatives. The problems were overcome by formulating an oral spray containing the TDL-Dexolve® complex. The need of today's era is to design industry and patient friendly formulation having better and immediate effect accomplishing the current regulatory guidelines. In context, the current work was aimed to formulate and optimize a newer oral spray of TDL with Vitamin D employing the Quality by Design (QbD) approach to provide a faster onset of action and better patient compliance. Another objective is to explore the Dexolve® as a multifunctional excipient and to assess the taste masking utilizing the BATA model.

2. MATERIAL AND METHOD

2.1. Materials

TDL was received from Intas Pharmaceuticals Pvt. Ltd., India. Dexolve® was a kind gift from Cyclolab, Budapest, Hungary. Vitamin D was procured from Intas Pharmaceuticals Pvt. Ltd., India. HPMC E-5 was procured from Merck Bioscience, India. The supplementary compounds used in the research were of analytical grade.

2.2. TDL-Dexolve® Complex

The TDL and ß-CD/Dexolve® inclusion complex, in the varied molar ratios, was formulated by the kneading method as per Table 1 [15]. The carrier was kneaded with a small quantity of water and ethanol (1:1) to form a slurry, and TDL was slowly added with trituration for one hour. The slurry was air-dried, pulverized, passed through sieve #100**,** and stored [16].

2.3. Characterization of Inclusion Complex

The inclusion complexes were evaluated for the phase solubility study [17], physical appearance [18], %yield [19], particle size [20]stability, bioavailability and consequently the therapeutic efficacy and safety profile. The main goal of this work was to evaluate the compatibility of KTZ with some excipients: corn starch, microcrystalline cellulose, colloidal silicon dioxide, lactose monohydrate and povidone, using differential scanning calorimetry and thermogravimetry (TG, and drug content [21]. The % yield should be high (>90%) to ensure the better efficacy of the process. The particle size should be less (<50µm)

Table 1. Composition and characterization of TDL inclusion complex (n==3)

Batches	TDL: Carrier	Solubility (mg/ml)	Gibbs free energy (KJ)	Fold increase in solubility	%yield	Particle size (µm)	Drug content (%)
TDL	-	0.065	-	-	-	-	-
A1 (TDL:β CD)	1:1	0.160	-10502.4	58.91	90.00±0.60	34.26±0.90	99.40±0.175
A2 (TDL:β CD)	1:2	0.231	-1048.52	88.50	90.85±0.53	35.24±0.58	100.03±0.02
A3 (TDL:β CD)	1:3	0.292	-650.71	113.91	90.77±0.67	35.92±0.50	99.25±0.03
A4 (TDL: Dexolve®)	1:1	21.80	-14975.3	334.33	91.55±0.48	33.94±0.05	100.02±0.02
A5 (TDL: Dexolve®)	1:2	8.860	-12657.8	136.01	90.81±0.62	35.20±0.58	99.72±0.02
A6 (TDL: Dexolve®)	1:3	1.610	-12275.5	117.25	91.84±0.77	35.29±0.52	98.36±0.05

and uniform for better processing and solubilisation. Particle size was determined accomplishing the microscopy method. The average particle size was calculated using calibrated microscope. Equivalent to 20 mg of TDLcomplex was taken and dissolved in pH 6.8 phosphate buffer solution, diluted suitably and measured for its absorbance with a UV spectrophotometer (UV-1900, Shimadzu Corporation) at 284nm. The amount of TDL was calculated from the standard plot. The TDL content should be in the range of 95-105% as per USP.

The phase solubility study was performed to estimate the fold increase in solubility and Gibb's free energy. An excess quantity of inclusion complex was mixed with 5ml water in a vial. The vials were sealed and kept in an orbital shaker for 72 h at 50 rpm and 37±0.5°C. The sample was then centrifuged to separate undissolved particles. The supernatant was taken, filtered, suitably diluted and estimated for the amount of TDL using a UV-visible spectrophotometer at 284 nm[22]especially tablets, have a broad market worldwide. Constraints of tablets are a long process, pollution, high processing cost, and requiring more excipient. The research was performed to optimize an eco-friendly immediate-acting pastille of TDL to put forward an alternate formulation to a tablet using advanced data mining tools. Another objective is to assess the taste masking of TDL using the Brief Access Taste Aversion (BATA. In addition to the solubility, the reaction's free energy (ΔG^o) was also calculated. The negative free energy was desired for the spontaneous reaction or solubilization. More negative value increases the spontaneous nature of the reaction. The fold increase in solubility was also measured with each molar ratio of the complex compared to the pure TDL [17].

Structural Analysis

The chemical structural determination was performed by Fourier Transform Infrared Spectroscopy (FTIR) study. TDL and complex structural determination was performed using the FTIR spectrophotometer (FTIR-WQF-520). TDL (1mg) and dry fined KBr (300 mg) were triturated, compressed under vacuum at a pressure of about 800MPs to form a compact disk, and scanned between 4000-250 cm^{-1}. The spectra were investigated for significant deviation in peaks of the functional groups [23].

Thermal Behaviour Assessment

The Differential Scanning Calorimetry (DSC) was able to observe the thermal behaviour of TDL and complex using a differential scanning calorimeter (Perkin Elmer, DSC-Pyris-1, USA). A sample (2mg) was held for 1min at 50°C and then heated gradually at 10°Cmin^{-1}. The onset of melting point and fusion enthalpy of samples were calculated. The conversion of crystalline to amorphous form was assessed [24].

Solid State Characterization

Scintag diffractometer (XGEN-4000, Scintag Corp., USA) was utilized to assess the amorphous nature of the substances. X-ray Diffractometry (XRD) pattern of TDL and the physical mixture was assessed. The sample was treated with Ni-filtered Cu Ka radiation. The radiation was of 45kV voltage and 40mA current and scanned at 2min over a diffraction angle of 2ɵ and a range of 3–70˚ [25].

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2.4. In-vivo BATA Model

The BATA model is preferred over other methods due to its numerous benefits. The BATA model accomplished a tachometer, which is a costly and delicate instrument. To overcome the problems, modified equipment was designed (Figure 2d). Four groups, consisting of 3 rodents, were chosen for study. Each rat was water-deprived for 22 hours before every period and kept in a tachometer for 40 minutes. The first group was exposed to TDL solution, the second with a solution of marketed TDL tablet (Megalis 10mg, Macleods Pharmaceuticals Ltd.), the third with TDL oral spray containing Vitamin D and other excipients, and the fourth with distilled water. The concentration of each solution was equivalent to TDL 10mg/ml. The institutional animal ethical committee at Anand Pharmacy College approved the study with suggested protocol (Letter No. - APC/2018-IAEC/1842). The data were analyzed using Prism software, and ANOVA analysis was performed using the Post Hoc Tukey test [22],[26],[27]in vivo and clinical data to evaluate the palatability of a novel midazolam chocolate tablet. In vitro dissolution experiments showed the crushed tablet to release within 5 min 1.68 mg of midazolam into simulated saliva. This translated to a drug level of 0.84 mg/ml in the oral cavity, which would be higher than the midazolam bitterness detection threshold concentration of 0.03 mg/ml determined in a rat 'brief access taste aversion' (BATA. The equation calculated the lick ratio:

$$Lick\ ratio = \frac{\text{Number of licks to each test solution}}{\text{mean number of licks to water}} * 100 \quad \text{.....Eq. 1}$$

2.5. Formulation of Oral Spray

The oral spray was formulated using HPMC E5 as a viscosity-imparting agent and ethanol: water as a solvent system. A weighed amount of HPMC E5 (0.5-1.5%) and TDL-Dexolve® complex (equivalent to 20 mg TDL per ml) was separately solubilized in water (55-65 ml) and ethanol (35-45 ml), respectively. Vitamin D (10µg per ml) was added into the non-aqueous phase. The water phase was slowly added to the organic phase with continuous stirring at 50 rpm for 15 min. The solution was filtered and filled in a container [28]9,13-trimethyl-4-tetradecenyl.

2.6. QbD

Quality Target Product Profile (QTPP) defines the safety and efficacy of the developing product, and it is directly linked to the drug labelling of the product [29]"ISBN":"3662546116","ISSN":"1999492 3","abstract":"Nanoparticle research and development for pharmaceuticals is a challenging task in the era of personalized medicine. Specialized and increased patient expectations and requirements for proper therapy adherence, as well as sustainable environment safety and toxicology topics raise the necessity of well designed, advanced and smart drug delivery systems on the market. These stakeholder expectations and social responsibility of pharma sector open the space and call new methods on the floor for new strategic development tools, like Quality by Design (QbD. The initial QTPPs were related to the route of administration (oral), dosage form (spray), and strength (20mg). Here, the QTPPs were chosen at the patient's convenience as justified in Table 2. Each quality attribute is assessed for its critical effect on product characteristics [30]. Based on the preliminary study and experience, drug release and spray pattern were considered critical quality attributes (CQAs) for the oral spray of TDL as depicted in Table 2. From the Ishikawa diagram (Figure 1) [31], the amount of HPMC E 5 and solvent composition were critical formulation variables as they significantly influenced chosen CQAs.

2.7. Optimization of Spray

A 3^2 complete factorial design encompassing nine batches was employed to optimize TDL spray as shown in Table 3. Design Expert software 13 was utilized to recognize the correlation between chosen dependent and independent variables. The amount of ethanol (X_1) and HPMC E5 (X_2) were chosen as formulation variables, whereas spray pattern (Y_1) and %drug release at 10min (Y_2) were picked as dependent variables. Multiple linear regression analysis (MLRA), examined by one-way ANOVA at 0.05 probability (P) level, was used to generate a model. Terms with a higher P-value (>0.05) were reflected as non-significant [32]biopharmaceutical classification class-III agent. Materials and Methods: SR tablets of pravastatin were prepared using variable amounts of hydroxy methyl propyl cellulose (HPMC. The influence of variables on responses can be observed using generated contour plots. Design space was generated using X_1, X_2, Y_1 and Y_2 constrains. Two checkpoints

Table 2. QTPPs and CQAs with their target and justification for TDL spray

QTPPs		
QTPPs	**Target**	**Justification/Explanation**
Dosage form	Spray	Pharmaceutical equivalence requirement: Same dosage form
Route of administration	Oral route	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength	20 mg	Pharmaceutical equivalence requirement: Same strength
CQAs		
CQAs	**Target**	**Justification/Explanation**
Physical Attributes	Colour and homogeneity acceptable to the patient. No visual defects should be there	Colour and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
Odour	Pleasant odour	In general, a noticeable odour is not directly linked to safety and efficacy, but odor can affect patient acceptability and lead to complaints. For this product, neither the drug substance nor the excipients have an unpleasant odor.
Taste	Pleasant taste	Taste is directly correlated to the patient's convenience as the formulation is targeted to the oral cavity. So, the taste is considered critical and needs to improve the taste of bitter drug before incorporating into the formulation.
Identification	Positive for drug substance	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity.
Release of drug	NLT 85% in 10 min	The release is considered a critical quality attribute as it directly affects the therapeutic effectiveness of the formulation
Spray pattern	9-11 cm	The maximum area should be covered for better absorption and thereafter bioavailability so considered as critical.

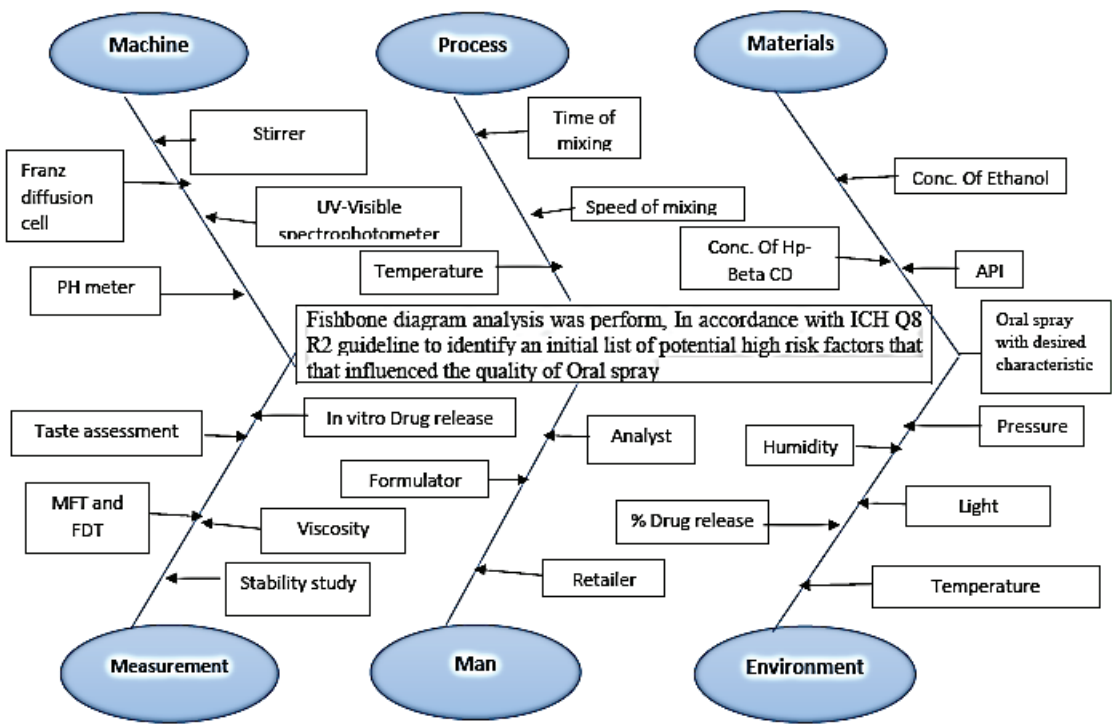

Figure 1. Ishikawa Diagram of TDL oral spray

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Table 3. Design matrix with responses and evaluation parameters of TDL spray

Batches	X1 (ml)	X2 (%)	Y1 (cm)	Y2 (%)	pH	Flame projection (cm)	Drug content (mg)	Weight per actuation (mg)
F1	45	1	7.5±0.01	87.78±0.3	6.7±0.004	9.1±0.20	25.55±0.02	0.68±0.004
F2	40	1	7.0±0.04	74.89±1.2	6.8±0.01	10.9±0.17	25.82±0.03	0.68±0.004
F3	40	0.5	10.0±0.12	85.01±0.8	6.7±0.008	10.9±0.11	23.08±0.03	0.68±0.004
F4	45	1.5	5.5±0.08	64.08±0.5	6.9±0.009	9.0±0.11	31.07±0.05	0.68±0.004
F5	35	1.5	4.0±0.09	54.98±0.4	6.7±0.004	11.8±0.15	18.81±0.06	0.68±0.004
F6	35	1	6.5±0.08	65.00±1.1	6.8±0.004	11.6±0.15	14.75±0.60	0.68±0.004
F7	45	0.5	10.5±0.16	94.10±2.1	6.8±0.01	9.5±0.05	32.70±0.10	0.68±0.004
F8	35	0.5	9.0±0.12	71.98±1.6	6.7±0.01	11.8±0.15	20.39±0.08	0.68±0.004
F9	40	1.5	4.5±0.24	59.05±1.2	6.7±0.01	10.8±0.20	23.78±0.05	0.68±0.004

and one optimum batch were chosen from the design space to validate the developed model [33]. The chosen batches were formulated, evaluated, and compared with the predicted values.

2.8. Evaluation of Oral Spray

pH of TDL spray

The pH meter (Welltronix Instruments Pvt. Ltd., India) was calibrated according to the manufacturer's directions. The probe tip was rinsed with water and dipped into the spray solution. The meter was permitted to equilibrate and note the pH in triplicate. The pH is an important parameter for the liquid formulation. A change in the pH of the solution directly affects the solubilization and precipitation of the drug [34]. The ideal pH of the formulation should be the same as that of the pH of the oral cavity.

Spray pattern

The oral spray of TDL was sprayed on a Whatman filter paper to quantify the spray pattern and area. The diameter of a spray was calculated for the spray area in triplicate [35].

Flame projection

It specifies the influence of spray on the extension at an exposed flame. The spray was squirted for 4 sec into a flame. The flame extension depends on the spray composition, and the length was observed using a triplicate ruler [36] calibration of microfossil datums to a magnetostratigraphy was limited to stratigraphical successions obtained from relatively short piston cores (generally less than 10 m.

TDL content

One ml of TDL spray was diluted and measured for its absorbance with a UV spectrophotometer (UV-1900, Shimadzu Corporation) at 284nm. The amount of TDL was calculated from the standard plot [37].

Average weight per actuation

The initial weight of the container was recorded. Five successive deliveries were sprayed from the container, and the container weighed again. The difference in weight is divided by the number of spray deliveries used to determine the average weight per dose. The procedure was performed for five containers [38].

Rheological behaviour

The viscosity of the prepared spray solution was measured using a Brookfield viscometer (LVDV II PRO+) at a shear rate of 10, 50, 100, and 200 rpm. The sample was placed in a beaker and equilibrated for 5 minutes before measuring. At each speed, the corresponding dial reading on the viscometer was recorded in triplicate [39].

In-vitro TDL release study

The *in-vitro* drug release study of optimized formulation was performed using a Franz diffusion cell integrating cellulose nitrate membrane. The release study aimed to assess the amount of diffusion through the membrane. Equivalent to 10mg of solvent was added into the donor compartment with pH 6.8 phosphate buffer solution. The assembly was adjusted to 37±0.5°C and 50 rpm to simulate the *in-vivo* condition. One ml sample was collected from the receptor compartment containing pH 7.4 phosphate buffer solution at a fixed interval time, suitably diluted, and measured for its absorbance at 284nm using a UV-visible spectrophotometer. The %CDR was calculated using a standard curve of TDL [40].

Stability study

TDL spray stability was evaluated as per ICH guidelines. The stability study of the optimum batch was carried out for six months at 40±2°C and 75%RH. The spray was evaluated for drug-related parameters like TDL content and its release behavior as well as physical properties like visual examination, spray area and pH [41].

3. Results and Discussion

3.1. Phase Solubility Study

The phase solubility study revealed that the 1:1 ratio of TDL: Dexolve® exhibits the highest solubility, maximum fold increase in solubility compared to TDL, and the highest negative free energy, reflecting the TDL solubilization's spontaneous nature. (Table 1). So, Dexolve® in a molar ratio of 1:1 was chosen for further work. The phase solubility diagram corresponds to the AL-type profile, indicating that Dexolve® was effective at one concentration only. It may be due to the high molecular weight of Dexolve®. If it was used in higher amounts, it retarded the solubilization and, therefore, the dissolution rate. Dexolve® is a beta sufobutyl ether beta-cyclodextrin sodium, a higher cyclodextrin derivative. It is a cyclic sugar-based molecule that enhances solubility due to its more hydrophilicity and better complex formation than other derivatives.

3.2. Characterization of Complex

The results of %yield, particle size, and drug content are shown in Table 1. The physical appearance of the prepared complex was found to be white and amorphous. The particle size, %practical yield, and drug content were observed to be 30-35 µm, more than 90%, and 95-100%, respectively.

Structural Analysis

The overlay FTIR spectra of TDL and complex are shown in Figure 2a. Broadening of the peak at 2800 to 3600cm^{-1} was observed in the spectra of the complex, which suggested stable hydrogen bond formation [42],[43]. It confirmed complex formation between the TDL and Dexolve® and enhancement in solubility of TDL.

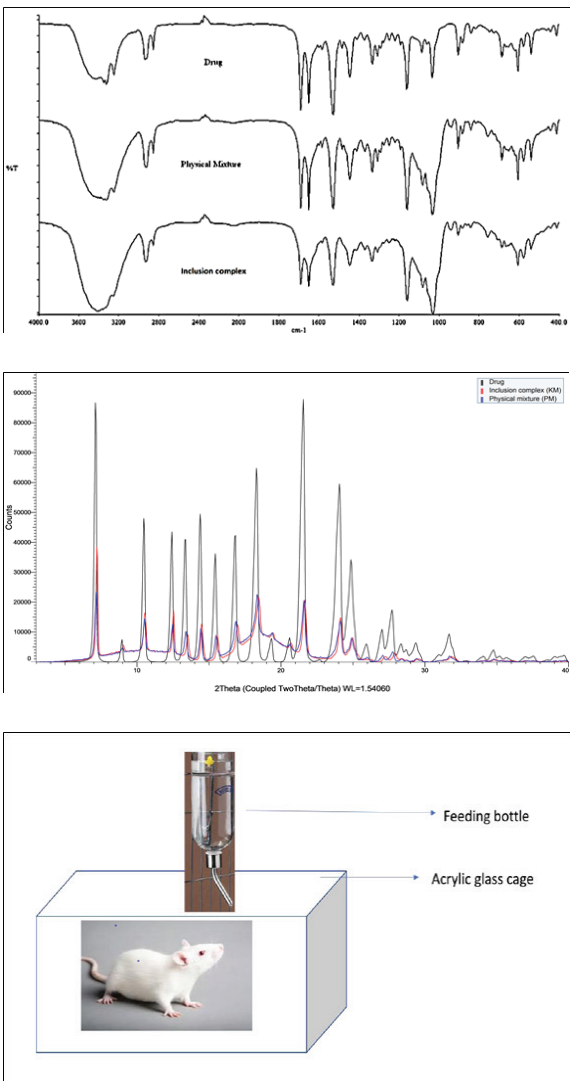

Figure 2. a) Overlay spectra of FTIR, b) Overlay spectra of DSC, and c) Overlay spectra of XRD spectra, d) Fabricated modified instrument for BATA study

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Thermal Behaviour Assessment

The DSC of the TDL and complex is depicted in Figure 2b. DSC study was performed to confirm the formation of the TDL-Dexolve® complex. The shifting of the peak and change in intensity, height and peak area confirmed the conversion of crystalline to amorphous structure. The sharp peak of TDL shifted from 303°C to 283°C. This conversion indicates the crystalline translation to an amorphous state, ultimately leading to higher solubility. The shifting of the peak may be due to the microenvironment melting of Dexolve at increased temperature, and thus solubilization of TDL resulted in the shifting of peak and reduction in intensity of peak,

Solid State Characterization

Figure 2c shows the XRD pattern of the TDL, physical mixture, and complex. The XRD pattern of the TDL shows intense crystal peaks. However, in the inclusion complex, the number and strength of peaks were decreased owing to the partial alteration of the crystalline structure to the amorphous structure.

3.3. In-vivo Taste Assessment

Statistical data analysis was done using one-way ANOVA with Post hoc Tukey's test employing graph pad prism 6.01. The lick ratio of water (control) was considered 100%, while 50% inhibition in the lick ratio indicates the bitter taste of medicament. The results show different lick ratios of 16, 88, and 81% for TDL, marketed formulation, and spray, respectively. It indicates no significant difference between marketed and spray formulations but had a significant difference with pure TDL (Table 4**).** The lick ratio above 80 indicates that taste masking was effective, and the bitter taste was masked entirely [22]especially tablets, have a broad market worldwide. Constraints of tablets are a long process, pollution, high processing cost, and requiring more excipient. The research was performed to optimize an eco-friendly immediate-acting pastille of TDL to put forward an alternate formulation to a tablet using advanced data mining tools. Another objective is to assess the taste masking of TDL using the Brief Access Taste Aversion (BATA. Results of ANOVA indicate a significant difference between TDL: marketed and TDL: Dexolve® inclusion complex shown in Table 4. In a nutshell, the taste of a formulated complex and a marketed product exhibits a comparable lick ratio that may be acceptable by the human volunteer. In addition, BATA model was considered efficient and economical in-vivo study compared to other taste masking study. It is also considered as an alternative to E-tongue and human taste panel. The model was also explored for other pediatric formulations.

3.4. Optimization of Spray

Table 3 shows nine batches with independent variables and the observed responses. The causal factor and response variables were related using a polynomial equation with statistical analysis. The approximations of response values based on the quadratic model were most suitable because its PRESS was the smallest. The polynomial equation consists of the coefficients for intercept, main effects, interaction, and

Table 4. Comparison by Tukey's multiple comparisons test of BATA model

Tukey's multiple comparison tests	Mean Diff.	95% CI of diff.	Significant?	Summary	P value
TDL vs. Complex	-392	-631.2 to -152.8	Yes	**	<0.05
TDL vs. Marketed	-429.3	-668.6 to -190.1	Yes	**	<0.05
TDL vs. Water	-500.7	-739.9 to -261.4	Yes	***	<0.05
Complex vs. Marketed	-37.33	-276.6 to 201.9	No	Ns	>0.05
Complex vs. Water	-108.7	-347.9 to 130.6	No	Ns	>0.05
Marketed vs. Water	-71.33	-310.6 to 167.9	No	Ns	>0.05

polynomial terms. A positive mark of co-efficient designates a synergistic influence, and a negative mark designates an antagonistic influence on the dependent variables.

Effect on response Y_1

The Design Expert software suggested a linear model with a high F value (439.29), R^2 value (0.995), and p-value (<0.001), indicating a good fit between the X_1 and X_2 with Y_1 (Table 5). It demonstrated that a minimum of one factor had a statistically crucial effect on Y_1. The inference was derived only from the main effect, not the interaction and polynomial terms. A drastic effect on Y_1 of the solution was shown by X_2. A slight change in X_1 can be observed in the change in the spray pattern. The 2D contour plots and 3D response surface plots are shown in Figures 3a and 3b for better understanding. The evolved mathematical model is:

Effect on response Y_2

The design expert software recommended a linear model with a high F value (37.87), R^2 value (0.997), and p-value <0.001, indicating a good fit between the independent variables and Y_2 (Table 5). It demonstrated that a minimum of one of the chosen factors had a statistically crucial influence on Y_2. The inference was derived only from the main effect, not the interaction and polynomial terms. A crucial effect on Y_2 was shown by X_1. The change in Y_1 can be obtained by slightly changing X_2. The X_2 is considered significant. The contour plot for Y_2 is shown in Figures 3c and 3d to enable the researcher to think. The desired value of % drug release should be >85% in 10min. The 2D and 3D response surface plots showed that as X_2 increases, Y_2 decreases. The evolved mathematical model is:

Overlay Plot

The overlay plot (Figure 3e) was designed by overlaying all the contour plots. The optimum values of the variables were obtained by graphical and numerical analyses using the Design-Expert software, which is based on the criterion of desirability. The yellow colour region indicates the optimal region. The optimized batch was selected based on the desired spray pattern and *in-vitro* drug release. The spray pattern should be spherical, and the covered area should be maximum. The % CDR should be more than 85% at 10 min.

Validation of Model

As shown in Table 5, the data revealed that the observed and predicted results are similar for selected

Table 5. ANOVA results and Validation of Model for TDL spray

ANOVA analysis							Validation of Model			
Factors	**Y_1**			**Y_2**						
	F-value	**P-value**	**Coefficient**	**F-value**	**P-value**	**Coefficient**	**Checkpoint batches**	**Optimized batch**	**Checkpoint batch I**	**Checkpoint batch II**
Model	154.20	0.0008	+7.00	37.87	0.006	76.00	**X_1 (%)**	41.33	41.375	41.71
X_1	48.00	0.006	+0.66	63.16	0.004	9.00	**X_2 (%)**	0.65	0.525	0.66
X_2	720.75	0.0001	-2.58	115.43	0.001	-12.17	**Y_1^P (%)**	9.00	9.70	9.00
X_1X_2	0.0000	1.00	+0.00	5.49	0.100	-3.25	**Y_1^o (%)**	9.60	10.02	8.60
X_1^2	0.0000	1.00	+0.00	0.00	1.000	0.00	**% Error**	6.66	3.29	4.4
X_2^2	2.25	0.23	+0.25	5.26	0.105	-4.50	**Y_2^P (%)**	85.00	86.94	85.00
R^2	0.9932			0.9285			**Y_2^o (%)**	87.70	82.00	88.00
Lack of fit	Non-significant			Non-significant			**% Error**	3.17	5.68	3.40

^{P}= Predicted value, ^{O} = observed value

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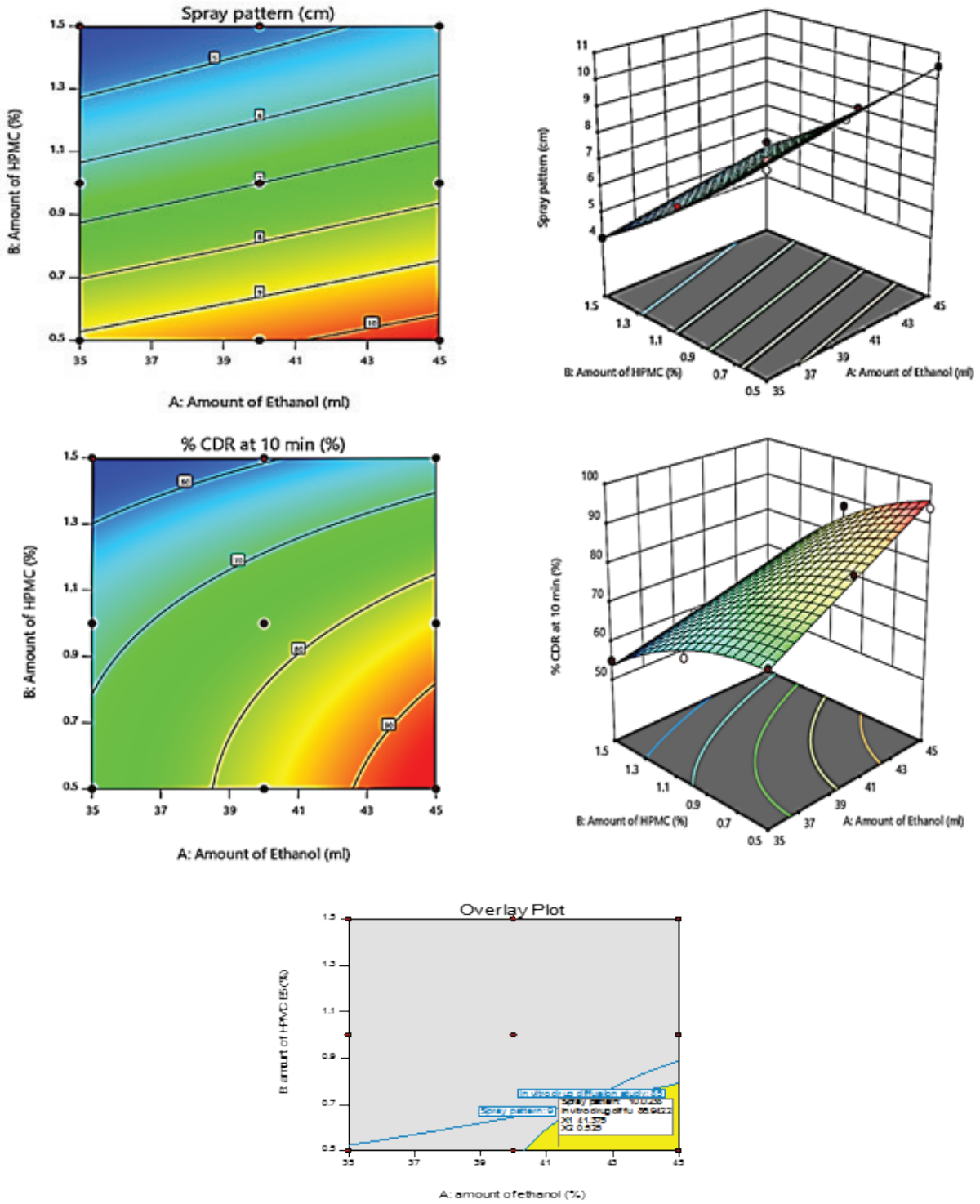

Figure 3. a) 2D plot of response Y1 b) 3D plot of response Y1 c) 2d plot of response Y2 d) 3d plot of response Y2 e) overlay plot

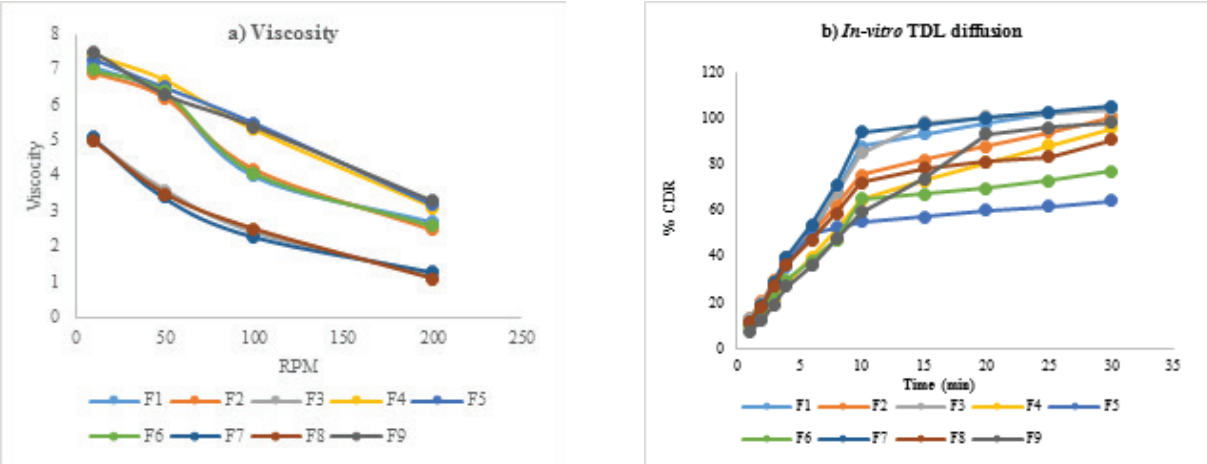

Figure 4. a) Viscosity determination b) In-vitro TDL release

batches. The % prediction errors were <10%, confirming that the model was highly accurate and predictive. All chosen compositions were evaluated for different characteristics and found to be within the anticipated range.

3.5. Characterization of Design Batches

The characterization results of various design batches are summarized in Table 3. The pH of the designed batches was between 6.7-6.9, closer to the buccal pH, indicating better stability and effectiveness. The spray pattern was spherical and uniform and covered a maximum area, leading to better uniformity, absorption, and immediate effect. The flame projection suggested that the extension of the flame increased with an increase in the amount of ethanol. The drug content was highest in batch F7 and lowest in batch F5. The results have suggested that an increase in ethanol drug content also increases. This is mainly owing to the higher solubility of the drug in ethanol.

Rheological Behaviour

Figure 4a shows the viscosity of prepared batches. The viscosity increased with an increasing amount of HPMC E5 and vice versa. The spray's viscosity decreased with increasing speed, suggesting the shear thinning system. It indicated the excellent delivery of content when the actuator was pressed.

In-vitro TDL Release

The release of TDL design batches was accomplished using pH 6.8 phosphate buffer in the donor compartment and pH 6.8 phosphate buffer in the receptor compartment for 30 minutes in a Franz diffusion cell integrating cellulose nitrate membrane. A significant effect was observed due to the change in the amount of HPMC (Figure 4b). The amount of ethanol was not significant for the TDL release pattern, but the amount of HPMC was considered significant for the TDL release pattern. As the amount of HPMC in-

Table 6. Stability data

Parameters	Initial	One month	Three months	Six months
Clarity	Clear	Clear	Clear	Clear
pH	6.8±0.02	6.7±0.1	6.7±0.05	6.7±0.02
Spray pattern	Spherical 9.60±0.1cm	Spherical 9.68±0.04cm	Spherical 9.58±0.02cm	Spherical 9.7±0.1cm
% TDL release in 10 min	85.24±0.33%	87.15±0.35%	84.29±1.2%	84±1.1%

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creases, drug release decreases. The optimized batch showed more than 90% TDL released in 10min.

Stability Study

The stability study of the optimum batch was carried out for six months at 40±2°C and 75% RH. The results indicated insignificant changes in clarity or appearance, pH, spray pattern, and % release, as shown in Table 6. Precipitation of inclusion complex was observed in the optimized formulation, neither at room temperature nor in refrigerated condition.

4. Conclusion

The recent pharmaceutical quality organization integrates the notions of quality metrics, pharmaceutical development (ICH Q8), quality risk management (QRM, ICH Q9), and pharmaceutical quality systems (ICH Q10). The oral spray formulation of TDL was systematically developed using water, ethanol, and HPMC E5 %. The addition of Vitamin D has the potential effect on the ED treatment. The amount of ethanol and HPMC E5 % significantly affected the formulation of an oral spray. One crucial outcome of the present study was to use environmentally friendly excipients to formulate the oral spray. The current formulation was designed accomplishing the need of patient and industry having immediate and better effect of TDL. The current formulation can be upheld to the industry.

Statement of Contribution of Researchers

Concept – H.R.; Supervision – H.T..; Resources H.T.; Data Collection and/or Processing – H.T..; Analysis and/or Interpretation –H.T..; Literature Search –H.R., V.T.; Writing –V.T., T.G..; Critical Reviews – T.G.

Conflict of Interest

The authors do not have any declarations of interest.

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