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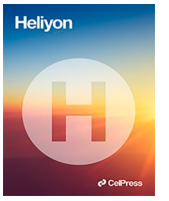

Research article

Investigating *in-vitro* functionality and *in-vivo* taste assessment of eco-friendly Tadalafil Pastilles

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ABSTRACT

Tadalafil (TDL) has poor bioavailability due to the less aqueous solubility and bitter taste. Oral solid dosage forms, 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) model. The amount of PEG-4000, Polyox N-10, and Kyron T-314 were chosen as critical material attributes from failure mode effect analysis. Box-Behnken design (BBD) was utilized to optimize the pastilles and ascertained the significant impact of chosen variables on disintegration time and % CDR at 10 min. The control strategy and optimal region were located using an overlay plot. The pastilles were able to release the drug within 15 min due to faster disintegration. The formulated pastilles were of uniform size, shape, and mechanical strength. The bitter taste of TDL was masked and confirmed by the BATA model. The newer formulation may be helpful in the industry due to its eco-friendly, single-step, and economical process. It unlocks a new direction in the field of oral solid dosage form as an alternative to tablets.

1. Introduction

Erectile dysfunction (ED) could be defined as the ineptitude to achieve or sustain an erection enough for desired sexual enactment [1,2]. Its occurrence increases drastically from about 6 % in the age group 20–29 years to 50–70 % in the age group 40–79 years. Its rate is projected to increase significantly to over 320 million by 2025 [3–5]. India is the feebleness capital of the world because of the high infection rate in the male reproductive system and more males [6–9].

Many treatments are available to treat ED [10,11]. phosphodiesterase-5 (PDE-5) inhibitors are the first-line treatment administered orally [12]. The most well-known of these PDE5 inhibitors are Sildenafil, TDL, Vardenafil, and Avanafil [13,14]. These medications inhibit PDE5, which keeps the level of cGMP high and promotes erections [15,16]. Compared to other PDE5 inhibitors, TDL has an immediate onset of action and the most extended duration of action [17–22]. TDL has limited bioavailability due to low aqueous solubility and bitter taste [23–26]. The poor aqueous solubility was overcome by formulating an eco-friendly pastilles formulation using the modified proposed method. The bitter taste was masked using a chocolate base. The pastilles are oral solid dosage forms

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intended to be used in the oral cavity made from solid lipids or hydrophilic bases.

Nowadays industry is focusing on the development of economic quality product with easy scale up process and better therapeutic outcome as well as patient compliance. This is the utmost requirement to reduce the overall production cost, to sustain patentability and better therapeutic outcome. Currently, the poor oral aqueous solubility has been overcome by formulating the solid dispersion or complex using a melting or complexation method and then it was converted into the final suitable dosage form for administration. These are widely used techniques for solubility enhancement due to their easy scale-up, validation, convenience, and economics [27–31]. In the current research, the emphasis was given to improve the solubility and formulating the desired formulation in the single step. The drug was unstable in gastric fluid. The problem was overcome by targeting the oral cavity. The bioavailability of the drug and patient compliance were improved by formulating the pastilles with the incorporation of a chocolate base, and the targeting of the oral cavity. Oral solid dosage forms, tablets, and capsules have the highest market share due to their enormous benefits [32–34]. However, it requires many excipients, complex and time-consuming processes, organic solvents, and dust generation [35]. An alternate innovative formulation was designed named pastilles to overcome these current limitations [36–39]. The unit solid dosage form is prepared using the lower melting point or waxy substances that are solidified and administered orally [40–43]. It has numerous industrial and social benefits over tablets [25,44,45]. The significant advantage of formulating the pastilles is using the concept of "Green chemistry," as there is no use of organic solvent, and no dust generation leads to less pollution [46,47].In a nutshell, the attempt was made to explore the environment and patient-friendly immediate-release formulation of TDL using a systematic approach. The secondary objective was to assess the taste masking of TDL using the BATA model.

2. Material and methods

2.1. Materials

TDL – a PDE5 inhibitor, was a kind gift from Intas Pharmaceuticals Pvt. Ltd., India. Soya lecithin [48] was used to improve solubility and was purchased from Merck India Pvt. Ltd., India. Kollicoat IR (75 % polyvinyl alcohol units and 25 % polyethylene glycol) [49], Ludiflash (84.0–92.0 % D-Mannitol, 4.0–6.0 % Kollidon® CL-SF, 3.5–6.0 % Polyvinyl acetate, 0.5–2.0 % water and 0.25–0.60 % Povidone) [50], and Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer) [51] provided by BASF India Pvt. Ltd., India which are used to increase the release rate from the pastilles. Kyron T314 (Polacrilin Potassium) [52] and Polyox N 10 (polyethylene oxide) [53] were used as disintegrants and were obtained from Corel Pharmachem, India, and Colorcon India Pvt. Ltd., India. The pre-mix chocolate base (Morde milk chocolate – M21, Morde Foods Pvt. Ltd., India), which is composed of cocoa powder, cocoa butter, sugar, and milk solids, was used in the study All other reagents are of analytical grade.

2.2. A modified method for enhancement of solubility and designing pastilles

In the conventional approach, the solubility of the drug by formulating solid dispersion or complex is improved initially, characterized, and then incorporated into the final formulation. This research explored a new modified method and eco-friendly dosage form. The novel method is a single-step process that formulates the final dosage form – Pastilles, which has enhanced solubility. The instrument and method are shown in Fig. 1. Initially, pre-weighed quantities of TDL, chocolate base (10 %), Soluplus (5 %), PEG 4000 (75–85 mg), Kyron T 314 (5–10 %), and Polyox N 10 (15–25 mg) were taken, sieved from a 100# sieve, and loaded into the in-house fabricated pastillator. The mixture was melted, mixed, and passed through the needle (needle gauge – 15, inert hole diameter – 1.5 mm) at a fixed dropping height (3 mm) to solidify on chilled glass surfaces. (4–6 °C). The formed pastilles were scraped and stored in air-tight containers. The effects of Ludiflash, Kollicoat IR, and Polyox N 10 were assessed in preliminary composition. Polyox N −10 was chosen for further study. The effect of Soya lecithin and Soluplus was observed for dissolution enhancement. Soluplus was chosen as a dissolution enhancer in design batches.

2.3. Quality by design (QbD)

QbD starts with the product's Quality Target Product Profiles (QTPPs). QTPPs are designed as per the needs of the patient and labeling requirements. It also considered the quality, safety, and efficacy of the pastilles [54–56]. Quality attributes were defined to achieve the QTPPs. Each quality attribute was analyzed for its risk and identified the criticality of that attribute. The quality attributes

Fig. 1. Pastillation process.

critical to formulating pastilles were chosen as responses to measure in the optimization design. Disintegration time and TDL release were considered critical quality attributes (CQAs) to formulate immediate-release pastilles [57–59]. QTPPs and CQAs were identified and shown in Table 1.

2.4. Risk assessment study for identification of CPPs and CMAs

The manufacturing variables, process parameters, and material attributes that affect the quality of the pastilles were identified based on experience and literature. The Ishikawa fishbone diagram was generated using SmartDraw software (Fig. 2). All the variables are divided into material, process, equipment, API characteristics, environmental factors, and evaluation parameters [60,61].

The qualitative risk assessment approach was chosen to identify critical factors. The Failure Mode Effect Analysis (FMEA) was performed to identify the critical manufacturing variables, material attributes, or process parameters. In the FMEA method, the risk priority number (RPN) is calculated using the occurrence (O), severity (S), and detectability (D) of the risk [62–69]. OSD rank was given in the range of 1–5 for each variable. The variable that scored more RPN was considered a significant influence on product quality[61,70,71]. The FMEA analysis is shown in Table 2. From the FMEA analysis, the amount of PEG 4000, Polyox N-10, and Kyron T-314 were chosen as independent variables, which significantly affect the chosen critical quality attributes, i.e., drug release pattern and disintegration time.

2.5. Experimental design

Response Surface Methodology (RSM) is a geometrical output of a response variable plotted as an operation of the independent factors. The BBD and central composite design are widely explored designs for optimization. BBD is more used because it is an independent quadratic design with no factorial design batches. The compositions were chosen in BBD from the midpoint of the edges of the working space and at the center [72–74]. In TDL pastille optimization, three formulations were chosen at three different levels and formed 17 compositions. The chosen variables were the amount of PEG 4000 (X_1 – 75 to 85 mg), Polyox N-10 (X_2 – 15 to 25 mg), and Kyron T-314 (X_3 - 5 to 10 %). Design Expert 11 software accomplished to generate a design matrix, analysis, and optimization of

Table 1
QTPPs and CQAs of TDL pastilles.

QTPPs			
QTPPs		**Target**	**Justification**
Therapeutic Indication		Erectile Dysfunction	TDL is used to prevent erectile dysfunction diseases in those at high risk. It belongs to the BCS Class-2 drug, and it inhibits PDE-5 and enhances erectile function by increasing the amount of cGMP.
Target Patient Population		Adult	Pharmaceutical equivalence requirements: Same patient population
Route Of Administration		Oral	The oral route is the most widely used route of administration.
Dosage Form		Pastilles solid for oral route	Pastilles of the uniform dosage form are required for administration in an oral route.
Dose		10 mg	Pharmaceutical equivalence requirements: Same patient dose
Stability		At least years at room temperature	The stability of pastilles is required to achieve the therapeutic potency of the drug and also the drug release rate.
CQAs			
CQAs	**Target**	**Is It CQA?**	**Justification**
Excipients	Excipients to increase solubility and stability of the formulation.	Yes	Excipients are a primary assurance for a better quality of formulations by altering the size, hydrophilicity of formulation, morphology at solid-state, and stability of the pastille's formulation.
Appearance	Color and shape should be acceptable to the patient.	No	Color, shape, and appearance were not linked to safety and efficacy. Therefore, it is not critical. The target is set to ensure patient acceptability.
Pastilles size/Specific Surface Area	Uniform size pastilles with a diameter of 2–3 mm	No	The size of pastilles is not a critical parameter related to micromeritics property.
Contact Angle	Should be greater than 90 %	No	The contact angle is critical for the uniform size, shape, diameter, and low property.
Structure [Crystalline/ Amorphous]	Stable Form [Crystalline/ Amorphous]	No	The crystalline or amorphous state of the API affects the Stability and release properties. It is critically related to efficacy and quality.
Dissolution	More than 90 % of drugs released in 15min	Yes	Solubility and dissolution have a remarkable influence on drug release. It directly affects the therapeutic efficacy.
Disintegration time	Not more than 1min	Yes	Disintegration time affects therapeutic drug efficacy.
Taste	Pleasant taste	Yes	Taste affects patient compliance, so there is a need to improve the taste.
Assay	It should be 95–105 %	Yes	The assay affects drug quality, safety, and efficacy. Process variables may affect the assay of the drug product. Thus, the assay was evaluated throughout product and process development.
Weight Variation	Should follow the pharmacopeial limits of the capsule.	Yes	Variability in weight variation affects safety and efficacy.

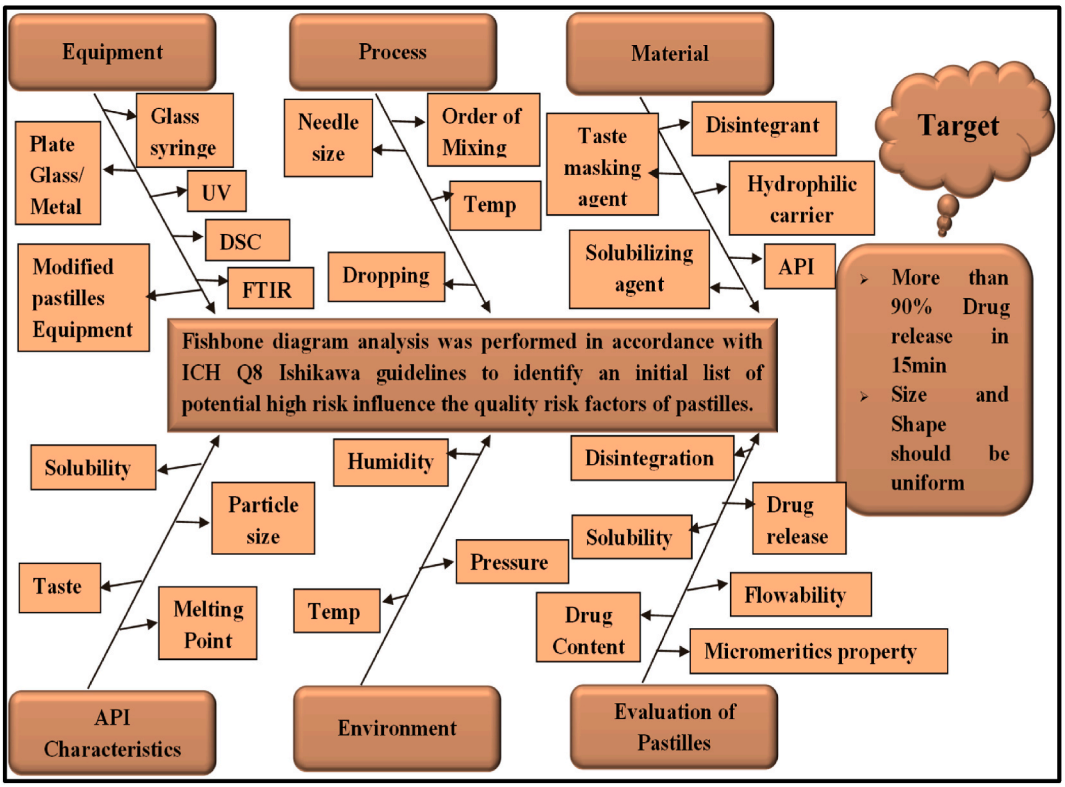

Fig. 2. Fishbone diagram of Pastilles manufacturing process.

pastilles. Seventeen compositions were formulated using a modified method and evaluated for responses like disintegration time (Y_1) and $^{\%\ CDR\ in\ 10\ min}$ (Y_2), as shown in Table 3. The quadratic model and polynomial equations were constructed for each response using ANOVA and MLRA. The significance of each term was identified using the back-elimination step process. In addition, the positive or negative effect of the variable was assessed. Contour and response surface plots are designed better to understand the correlation between the formulation variables and responses. The contour plot of the response was overlaid on each other to construct an overlay plot and to find the design space. The grid search analysis is integrated to analyze the predictive ability of the developed model.

2.6. Pre-formulation evaluation parameter

The pre-mix of pastilles formulation was assessed using the different micromeritic characteristics.

2.7. Weight variation

Weight variation was determined by choosing ten pastilles randomly. Pastilled were weighed, and the average weight was determined. The single pastille weight is compared with the average weight, and the % weight variation is calculated. Weight variation was considered as one of the CQA. The process parameters were kept constant during the formulation to avoid variation and errors. Only up to two pastilles should be out of the limit [75].

$$\%\ \text{Weight deviation} = 100\left(\frac{Average\ Weight - Individual\ Weight}{Average\ Weight}\right) \quad \text{Equation 1}$$

2.8. Uniformity of Dimensions

The uniformity of pastilles was determined in terms of thickness and diameter. It was measured using a thickness gauge. The test was performed in triplicate to reduce measurement error.

2.9. Friability

The friability was accomplished to measure the friability of pastilles. Preweighed pastilles were taken into the friabilitor, rotated at 100 rotations for 4 min, dedusted, and reweighed. There should not be too much weight loss. The friability value should be <1 % [76].

Table 2
FMEA analysis of Pastilles formulation.

	Failure mode	Impact of change	Occurrence	Route of failure	Severity	Control Measure	Detection	RPN	Rank
Material	**Conc. of disintegrants**	**Dissolution, Disintegration**	**5**	**Different Concentrations, Material Variation**	**5**	**Dissolution tester, Disintegration tester**	**5**	**125**	**1**
	Conc. of dissolution enhancer	**Dissolution, Disintegration**	**5**	**Different Concentrations, Material Variation**	**5**	**Dissolution tester, Disintegration tester**	**5**	**125**	**1**
	Conc. of hydrophilic carrier	**Pastilles quality**	**5**	**Different Concentrations, Material Variation**	**5**	**Dissolution tester, Disintegration tester**	**5**	**125**	**1**
	Taste masking agent	Pastilles quality	1	Different Concentrations, Material Variation	1	BATA model	1	1	11
Environment	Humidity	Pastilles quality	1	Change in atmospheric condition	1	Hygrometer	1	1	11
	Pressure	No effect	1	Change in atmospheric condition	1	Manometer	1	1	11
	Temperature	Pastilles quality	1	Change in atmospheric condition	1	Thermometer	1	1	11
Evaluation of pastilles	Drug release	Dissolution	4	Machine Failure, Poor Development	5	Dissolution tester	5	100	2
	Disintegration	Disintegration	4	Machine Failure, Poor Development	5	Disintegration tester	5	100	2
	Solubility	Dissolution	4	Machine Failure, Poor Development	5	Dissolution tester	5	100	2
	Flowability	Poor pastilles quality	3	Machine Failure, Poor Development	1	Carr's Index, Angle of Repose	3	9	9
	Micromeritics Property	Poor pastilles quality	3	Machine Failure, Poor Development	1	Carr's Index, Angle of Repose	3	9	9
Equipment	Modified pastilles equipment	Pastilles quality	3	Operator's Error, Equipment failure	1	Validation	1	3	10
	Dissolution apparatus	Dissolution	4	Operator's Error, Equipment failure	3	Validation	1	12	8
	UV Spectrophotometer	Drug estimation	3	Operator's Error, Equipment failure	3	Validation	1	9	9
	DSC	Drug estimation	3	Operator's Error, Equipment failure	3	Validation	1	9	9
	FTIR	Drug estimation	3	Operator's Error, Equipment failure	3	Validation	1	9	9
	Glass syringe	Pastilles quality	3	Operator's Error, Equipment failure	1	Validation	1	3	10
	Plate glass/metal	Pastilles quality	3	Operator's Error, Equipment failure	1	Validation	1	3	10
API Characteristics	Solubility	Dissolution	4	Machine Failure, Poor Development	3	Dissolution apparatus	1	12	8
	Particle size	Pastilles quality	3	Machine Failure, Poor Development	3	Optical measurement, sieve analysis	1	9	9
	Melting Point	Pastilles quality	3	Machine Failure, Poor Development	3	Melting point assembly	3	27	6
	Taste	No effect	1	Manual error	1		1	1	11
Process	order of mixing	Non-uniform mixing	3	Machine Failure, Poor Development	3	Automation of machine	1	9	9
	Needle size	Pastilles quality	3	Machine Failure, Poor Development	3	Automation of machine	1	9	9
	Dropping	Pastilles quality	3	Machine Failure, Poor Development	3	Automation of machine	1	9	9
	Temperature	Pastilles quality	3	Machine Failure, Poor Development, Operator's Error	3	Automation of machine	1	9	9

Table 3
Design Matrix with its responses to Pastilles.

Batch	X_1 (mg)	X_2 (mg)	X_3 (%)	Y_1 (Sec)	Y_2 (%)
F1	75	15	7.5	317	89.58
F2	85	15	7.5	310	97.95
F3	75	25	7.5	335	69.24
F4	85	25	7.5	329	89.97
F5	75	20	5	412	86.32
F6	85	20	5	397	96.14
F7	75	20	10	356	86.64
F8	85	20	10	292	95.72
F9	80	15	5	390	94.26
F10	80	25	5	394	90.52
F11	80	15	10	299	94.7
F12	80	25	10	305	90.61
F13	80	20	7.5	314	92.82
F14	80	20	7.5	350	85.17
F15	80	20	7.5	314	92.92
F16	80	20	7.5	315	91.74
F17	80	20	7.5	316	92.02

Friability was calculated using the following equation (2):

$$\%\ \boldsymbol{Friability} = \left(\frac{\mathrm{Wi} - \mathrm{Wf}}{\mathrm{Wi}}\right) * 100 \qquad \text{Equation 2}$$

W_i was the weight of the pastilles before the test, and W was the weight of the $_f$ pastilles after the test. A friability study was performed three times to reduce the errors.

2.10. Drug content

Ten pastilles were weighed, and the average weight was calculated. All the pastilles were crushed and powdered. Equivalent to 10 mg of drug was dissolved in 10 ml of methanol, and the volume was make-up to 100 ml with pH 6.8 phosphate buffer. The solution was shaken for 1 h and kept for 24 h. A 1 ml solution was taken from the stock solution in a 10 ml volumetric flask, and the volume was made with pH 6.8 phosphate buffers. The solution was filtered, and absorbance was measured spectrophotometrically at 284 nm against pH 6.8 phosphate buffer as a blank using a UV double beam spectrophotometer (UV 1800-PC, Shimadzu, USA) [77].

2.11. In-vitro dissolution study

The drug release study was accomplished using the USP type I apparatus. The dissolution medium was 900 ml of 6.8 phosphate buffer at 37 ± 0.5 °C. The rotation speed was kept at 50 rpm. At a pre-determined time, the solution (5 ml) was withdrawn and replaced with a blank buffer to maintain the same volume and sink condition. The solution was filtered with Whatman filter paper to remove the undissolved particles. The solution was analyzed for its absorbance using a UV spectrophotometer at 284 nm. TDL release was statistically calculated, and its relation with time (min.) was observed [78–80].

2.12. Differential scanning calorimetry (DSC)

DSC was performed using the Differential scanning calorimeter (PerkinElmer 8000, Netherlands) to assess the thermal behavior of the drug as well as the final formulation. The sample (2 mg) was kept in the holder at 50 °C, then increased gradually at 10 °C min^{-1}. The onset of the drug and formulation's melting point and fusion enthalpies were observed using DSC spectra. The drug's DSC spectra change indicates the drug's interaction with excipients [81,82].

2.13. Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy assessed the interaction between drug and excipients via functional group determination. The FTIR spectrometer was used to study the FTIR spectra. Initially, the disc was formulated with high pressure (800 MPs) from the triturated mixture of potassium bromide (300 mg) and sample. The disc was then placed in an FTIR spectrometer, scanned between 4000 and 250 cm^{-1}, and observed for functional group peak modification [81,83].

2.14. Prediction of in-vivo data from in-vitro data

The Wagner-Nelson method calculates *in-vitro* dissolution data from an *in-vivo* plasma drug concentration time profile. The back-calculation of the Wagner-Nelson method is therefore used to predict *in-vivo* plasma drug concentration-time profiles from the

dissolution data of optimized formulation. For this conversion, different reported pharmacokinetic parameters of TDL were used [84–87]. The equation for the same is as follows:

$$C_{t+1} = \frac{\left(\frac{2\Delta FD}{V_d}\right) + C_t(2 - K_e\Delta t)}{(2 + K_e\Delta t)} \quad \text{Equation 3}$$

Where, Ct+1 = Predicted Plasma Concentration at time t+1, D = Dose of drug administered, Vd = Apparent volume of distribution, Ct = Plasma Concentration at time t, ΔF = Fraction of dose absorbed, Δt = Time interval between t and t+1, Ke = Elimination rate constant of the drug.

2.15. Stability study

The stability of the pastilles was performed as per the accelerated stability testing guideline of ICH. The optimized composition of TDL pastilles was kept in a stability chamber (Nihar Instruments Pvt. Ltd., India) at 40±2°C and 75 ± 5%RH. The aesthetic characteristics, TDL content, and release were observed for specific intervals until six months [88,89].

2.16. In-vivo taste assessment - Brief Access Taste Aversion (BATA) model

Taste masking was assessed using techniques like a human taste panel, e-tongue, and animal models. This research explored the *in-vivo* taste aversion (BATA) model to assess the taste masking of the bitter drug TDL due to its numerous advantages. The BATA model was accomplished using a lab-scale fabricated lickometer as shown in Fig. 3. [90]. Lickometer was constructed using acrylic glass and stainless steel 316. The activity was observed using the attached camera on the upper side [91].

Four groups of rodents were chosen to perform the study. Each group contains three rodents. Rodents were deprived of water for 24 h before the study. The study was performed for 40 min. One group was treated with TDL solution, the second with Pastilles solution, 3rd with marketed formulation (Megalis 10 mg, Macleods Pharmaceuticals Ltd.) solution, and the fourth with water. The concentration of each solution was equivalent to TDL 10 mg/ml. The lick ratio was calculated for each group [90]. This work was recommended by the institutional animal ethical committee at Anand Pharmacy College (**Protocol Number: APC/2021-IAEC/2101**). Rodent aversion data was analyzed using graph pad Prism software and ANOVA analysis with the Post Hoc Tukey test. A p-value less than 0.05 is considered significant.

$$Lick\ Ratio = \frac{No.\ of\ licks\ to\ test}{Mean\ no.\ of\ licks\ to\ water} * 100 \quad \text{Equation 4}$$

2.17. Comparison of TDL pastille with marketed formulation

TDL-optimized pastilles were compared with the marketed formulation of TDL in terms of in-vitro functionality. The disintegration time and dissolution study were performed for both formulations. In addition, the process of tablet manufacturing and pastille manufacturing was compared.

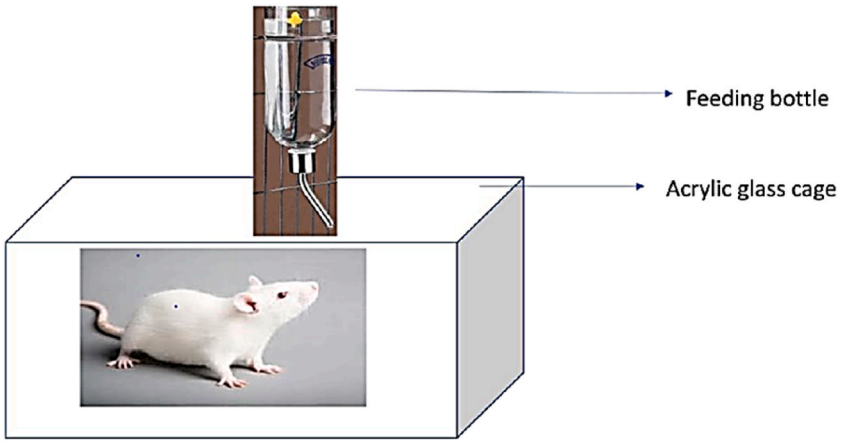

Fig. 3. Fabricated modified instrument of BATA model.

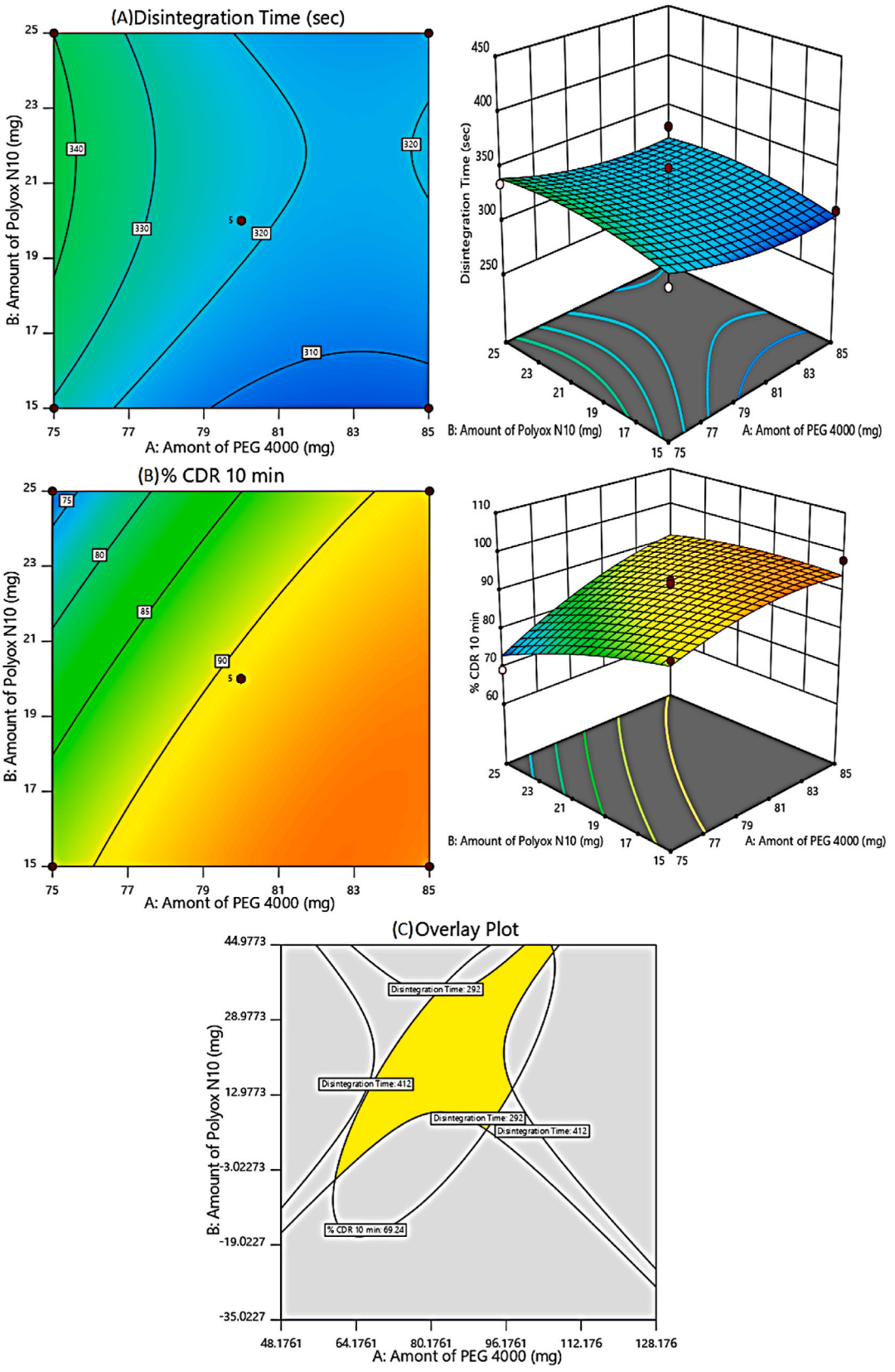

Fig. 4. A) Contour Plot & response surface plot of response Y_1, B) Contour Plot & response surface plot of response Y_2 and C) overlay plot.

3. Results and discussion

3.1. Experimental design

Response Surface Methodology (RSM) and BBD optimize TDL pastilles. Seventeen batches were designed in the BBD matrix using the Design Expert 11 version. Design batches were formulated using a modified method to accomplish the fabricated pastillator. Pastilles were evaluated for their chosen response, and results were incorporated into the software. ANOVA and MLRA were performed on the observed results of chosen responses. A quadratic model was generated for each response. A polynomial equation was generated for each response, including main, interaction, and polynomial terms.

Response Y_1

A quadratic model was developed by the software based on the ANOVA analysis (see Fig. 4). The analysis is shown in Table 4 in the form of F and P values. High model linearity factor value and F value with less p-value for disintegration time signpost the high predictability and significance of the model for response Y_1. The generated model identified the variance in the effect of each excipient amount. It was observed due to the high linearity factor (R^2 -0.9285). The amount of Kyron T-314 significantly affects the disintegration time. It influenced negatively on the disintegration time. Kyron t-314 is the cross-linked polymer of polycarboxylic acid with potassium ions. It is mainly due to the high swelling tendency on the hydration of Kyron. Kyron is responsible for faster disintegration without the formation of lumps [92]. Due to the formation of smaller particles, the dissolution of TDL was also increased. The amount of PEG 4000 and Polyox N 10 has little or no significant effect on disintegration time. PEG and Polyox are hydrophilic and thus help in the disintegration time to some extent [93]. From the polynomial equation (Equation (5)), the amount of PEG and Kyron negatively influenced disintegration time. 2-D contour plots and 3-D response surface graphs (Fig. 4) were generated to understand the effect of each variable on disintegration time.

$$Y_1 = +321.8 - 11.5A + 5.87B - 42.62C + 0.25AB - 12.25AC + 0.5BC - 9.1A^2 - 8.15B^2 + 33.35C^2 \quad \text{Equation 5}$$

Response Y_2

A quadratic model was developed by the software based on the ANOVA analysis. The analysis is shown in Table 4 as F-value and P-value. High model linearity factor value and F value with less p-value for dissolution profile signpost the high predictability and significance of the model for response Y_1. The generated model identified the variance in the effect of each excipient amount. It was observed due to the high linearity factor (R^2 -0.8399). The amount of Polyox N 10 and PEG significantly positively affected drug release. Polyox negatively influenced drug release. Polyox N 10 is a water-soluble resin of a long polyethylene oxide chain with a high molecular weight. Due to its resinous and film-forming nature, it slightly reduces the drug release but helps maintain the pastilles' structural integrity [94]. PEG has several hydroxyl groups in the structure, so it modifies the drug release profile [53]. It positively affected the drug release. The role of Kyron in the formulation is super disintegrant. Thus, it leads to pastilles' disintegration, smaller particles' formation, and faster drug release. In addition, the exact impact was also observed with the help of contour and response surface plots (Fig. 4).

$$Y_1 = +90.93 + 6A - 4.51B + 0.05C + 3.09AB - 0.185AC - 0.08BC - 2.78A^2 - 1.46B^2 + 3.05C^2 \quad \text{Equation 6}$$

3.2. Overlay plot of design

The contour plots of responses Y_1 and Y_2 were superimposed on each other, and the optimum region was identified. The optimum region was generated based on each response's desirability criteria. The researcher or industrialist can select any batch from the optimum region. The optimum region is also called design space. One optimum composition of pastille was chosen based on desirability value. The quadratic model was validated using the grid search analysis method. The calculated parentage prediction error was less than 2 % (Table 5), indicating that the model was validated for its statistical measurement and prediction.

Table 4
ANOVA analysis.

Term	R_1			R_2		
	Co-efficient	F-value	P- value	Co-efficient	F-value	P-value
Model	321.80	10.10	0.003	90.93	4.08	0.04
A	−11.50	4.41	0.07	6.00	18.65	0.004
B	5.87	1.15	0.32	−4.51	10.58	0.01
C	−42.62	60.65	0.001	0.05	0.002	0.97
AB	0.25	0.00	0.98	3.09	2.47	0.16
AC	−12.25	2.50	0.16	−0.19	0.01	0.93
BC	0.50	0.004	0.95	0.09	0.002	0.97
$_A$2	9.10	1.45	0.27	−2.78	2.11	0.19
$_B$2	−8.15	1.17	0.32	−1.46	0.59	0.47
$_C$2	33.35	19.54	0.003	3.05	2.54	0.15
R^2	0.9285			0.8399		
Lack of fit	0.5111			0.2491		

Table 5
Validation of the Quadratic model.

Terms	Optimized Batch	Check Point Batch 1	Check Point Batch 2
X_1 (mg)	85	85.32	83.34
X_2 (mg)	15	20.96	19.98
Predicted Y_1 (%)	310	346.52	342.12
Observed Y_1 (%)	308	342.50	341.12
% Error	0.64	1.15	0.29
Predicted Y_2 (%)	97.95	94.37	94.17
Observed Y_2 (%)	96.15	93.12	93.16
% Error	1.84	1.32	1.07

3.3. Pre-compressional parameters

Pre-compression parameters were evaluated to check the flowability of the powder mixture. The design batches were subjected to these tests as per the USP process. The results are depicted in Table 6. The results of each design batch showed excellent flow properties.

3.4. Post-formulation parameters

The results of post-formulation parameters are shown in Table 7. Friability is the indication of the structural integrity of the pastilles. The observed friability of all design batches and the optimum batch was 0.2–0.43 %. The results indicate that the formulated pastilles were mechanically strong enough to withstand the frictional force. The formulated pastilles were of uniform weight and size. The physical parameters of the pastilles were controlled by creating the same pressure on the liquid surface. TDL content was observed in the range of 98–100 %. Better drug content was achieved due to the excellent flow property of the powder, uniform heating, and maintaining all the instrument specifications at a constant level.

3.5. Disintegration time

Disintegration time is the crucial characterization parameter for the IR pastilles of TDL. The observed disintegration time was less than 7 min for design batches and optimal composition. Low disintegration time was observed mainly due to the combined effect of PEG 400, Polyox N 100, and Kyron T −341. PEG 4000 and Polyox N-100 are hydrophilic, helping to accelerate the disintegration or solubilization of pastilles. Kyron T-341 acts as a super disintegrate, resulting in faster disintegration due to high swelling when coming into contact with aqueous media.

3.6. In-vitro dissolution study of TDL pastilles

In-vitro drug release directly affects the bioavailability and therapeutic efficacy of the product. The dissolution study of the TDL pastilles was performed per the pre-specified procedure. The solution was withdrawn, filtered, diluted, and measured for absorbance. The amount of drug release was calculated from the absorption values using standardization data of TDL. The results are shown in

Table 6
Micromeritic properties of pastille pre-mix.

Batch	Angle of response (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index	Hausners' Ratio	Flowability
F1	9.33 ± 0.94	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F2	7.67 ± 0.47	1.09 ± 0.03	1.22 ± 0.03	10.91 ± 0.27	1.12 ± 0.003	Excellent
F3	8.70 ± 0.66	1.17 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F4	8.66 ± 0.47	1.22 ± 0.03	1.40 ± 0.04	12.25 ± 0.35	1.14 ± 0.004	Excellent
F5	8.87 ± 0.84	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F6	7.00 ± 0.83	1.22 ± 0.03	1.40 ± 0.04	12.25 ± 0.35	1.14 ± 0.004	Excellent
F7	8.33 ± 0.47	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F8	7.67 ± 0.47	1.17 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.07 ± 0.002	Excellent
F9	9.33 ± 0.47	1.18 ± 0.06	1.34 ± 0.06	11.79 ± 0.57	1.13 ± 0.007	Excellent
F10	7.33 ± 0.94	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F11	9.00 ± 0.81	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.57	1.13 ± 0.007	Excellent
F12	5.67 ± 0.47	1.14 ± 0.08	1.28 ± 0.10	11.38 ± 0.83	1.12 ± 0.011	Excellent
F13	9.60 ± 0.43	1.13 ± 0.03	1.28 ± 0.04	11.33 ± 0.30	1.12 ± 0.003	Excellent
F14	8.33 ± 0.47	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.57	1.13 ± 0.007	Excellent
F15	9.33 ± 0.47	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F16	9.00 ± 0.81	1.18 ± 0.06	1.34 ± 0.07	11.79 ± 0.56	1.13 ± 0.007	Excellent
F17	9.60 ± 0.43	1.13 ± 0.03	1.28 ± 0.04	11.32 ± 0.31	1.12 ± 0.003	Excellent
Optimum batch	8.33 ± 0.47	1.09 ± 0.02	1.22 ± 0.03	10.92 ± 0.27	1.12 ± 0.003	Excellent

Table 7
Physicochemical characteristics of design batches.

Batch	Friability (%)	Diameter (mm)	Thickness (mm)	Weight (mg)	TDL Content (%)	Disintegration Time (sec.)
F1	0.27 ± 0.005	5.20 ± 0.1	2.67 ± 0.47	68.88 ± 0.57	99.89 ± 0.01	317.33 ± 0.57
F2	0.43 ± 0.01	7.16 ± 0.01	3.00 ± 0.01	83.14 ± 0.05	99.39 ± 0.01	310 ± 1
F3	0.20 ± 0.01	5.10 ± 0.1	2.67 ± 0.47	71.19 ± 0.02	99.79 ± 0.01	335 ± 1
F4	0.42 ± 0.01	7.30 ± 0.1	2.33 ± 0.47	75.95 ± 0.14	99.86 ± 0.057	329 ± 1
F5	0.26 ± 0.01	5.13 ± 0.01	2.33 ± 0.47	66.64 ± 0.31	98.93 ± 0.01	411 ± 1
F6	0.43 ± 0.005	7.20 ± 0.15	2.33 ± 0.47	96.46 ± 0.01	98.93 ± 0.01	397 ± 1
F7	0.37 ± 0.005	5.23 ± 0.01	2.67 ± 0.47	70.21 ± 0.30	99.61 ± 0.01	355.66 ± 0.57
F8	0.43 ± 0.01	7.23 ± 0.01	2.67 ± 0.47	74.66 ± 0.02	99.86 ± 0.057	291.33 ± 1.15
F9	0.37 ± 0.005	6.53 ± 0.01	2.33 ± 0.47	80.46 ± 0.01	99.12 ± 0.01	390 ± 1
F10	0.43 ± 0.01	6.82 ± 0.005	2.33 ± 0.47	81.12 ± 0.62	98.54 ± 0.01	394 ± 1
F11	0.27 ± 0.01	6.76 ± 0.01	2.33 ± 0.47	87.37 ± 0.63	99.86 ± 0.057	299 ± 1
F12	0.43 ± 0.01	6.86 ± 0.01	3.00 ± 0.01	90.46 ± 0.02	98.54 ± 0.01	305 ± 1
F13	0.26 ± 0.005	6.46 ± 0.01	2.33 ± 0.47	84.54 ± 0.05	99.8 ± 0.01	313.66 ± 0.57
F14	0.43 ± 0.01	6.56 ± 0.01	3.00 ± 0.01	84.54 ± 0.05	99.86 ± 0.057	350 ± 1
F15	0.36 ± 0.005	6.63 ± 0.01	3.00 ± 0.01	84.54 ± 0.05	99.12 ± 0.01	314 ± 1
F16	0.42 ± 0.005	6.70 ± 0.1	3.00 ± 0.01	84.54 ± 0.05	98.74 ± 0.01	315 ± 1
F17	0.27 ± 0.01	6.56 ± 0.05	2.67 ± 0.47	84.54 ± 0.05	99.51 ± 0.01	316 ± 1
Optimized Batch	0.27 ± 0.01	6.53 ± 0.005	2.67 ± 0.47	80.46 ± 0.01	99.52 ± 0.01	310 ± 1

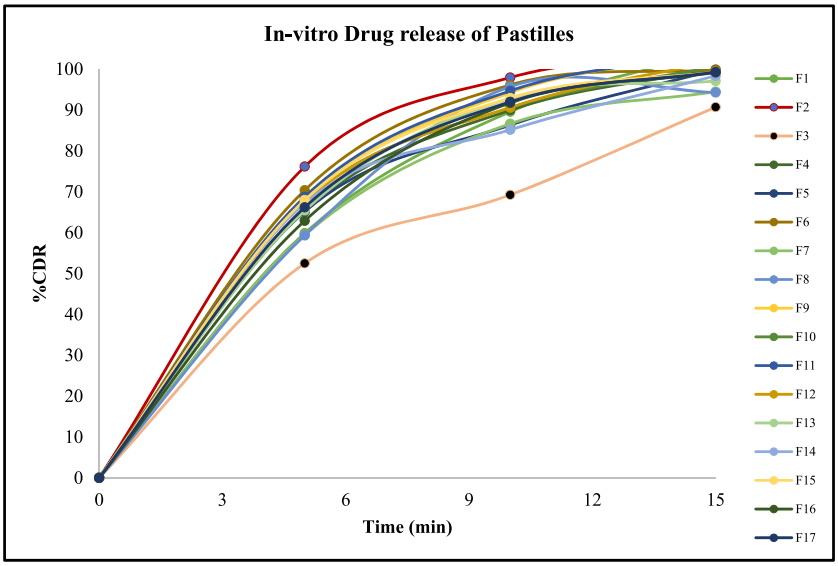

Fig. 5. *In-vitro* Drug release of Pastilles.

Fig. 5. The results indicated the significant influence of PEG 4000, Kyron T-314, and Polyox N 10 on TDL release. PEG 4000 and Kyron T −314 positively impacted the TDL release. It is mainly due to its polar nature and structural modification in the presence of aqueous media. Formulated pastilles were able to release the TDL within 1 h.

3.7. DSC study of TDL and pastilles

The DSC spectra of the TDL and pastilles are shown in Fig. 6. The DSC spectra confirm the physical change in the TDL structure. The DSC spectra indicate the conversion of TDL from crystalline to amorphous structure. The solubility and dissolution were enhanced due to the structural transition [95]. DSC spectra show a sharp endothermic peak at 300.5 °C, corresponding to the melting point of TDL. The disappearance of the peak at 300.5 °C confirms the conversion of the crystalline drug to an amorphous form [96]. The new peak, which appears at 56.7 °C, corresponds to the melting point of PEG.

3.8. FTIR study of TDL and pastilles

FTIR spectra are shown in Fig. 7. The FTIR spectra confirm the H-bond formation between the drug and excipients. The additional peak was observed at 3425 cm^{-1}, corresponding to the hydroxyl group formation [97,98].

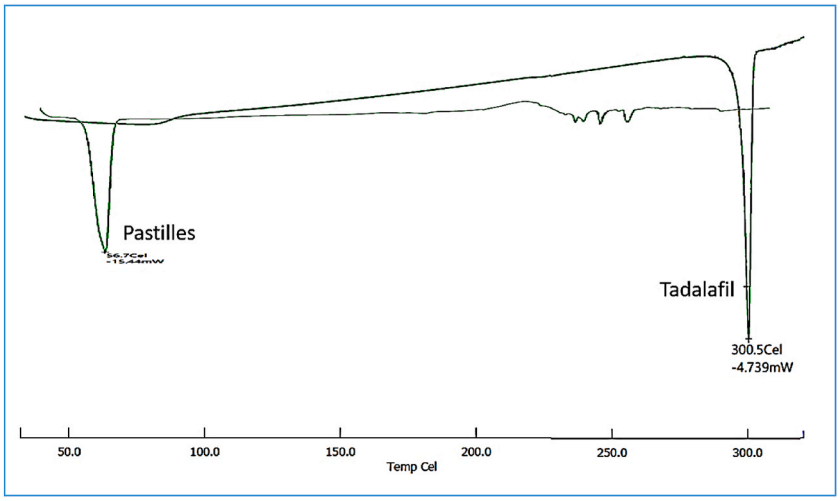

Fig. 6. DSC spectra of TDL and Pastilles.

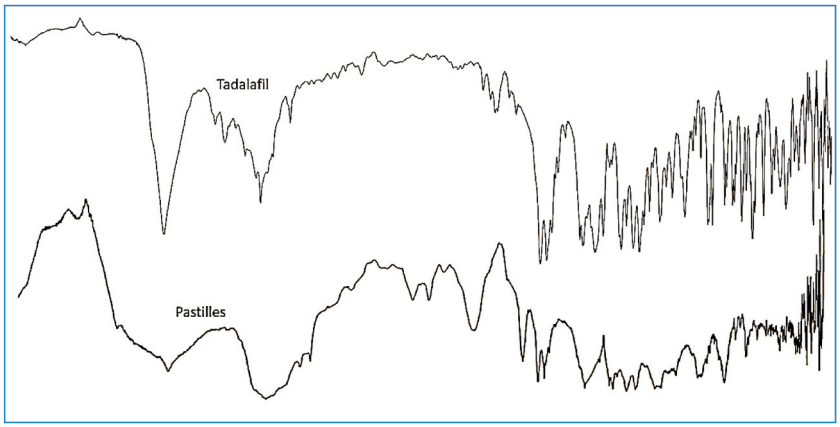

Fig. 7. FTIR spectra of TDL and pastilles.

3.9. *In-vivo prediction*

Convolution and back calculation of the Wagner-Nelson approach was used to predict the plasma concentration-time profile from *the in-vitro* dissolution data of the optimized batch [87]. The PK parameters C_{max} (126.22 ng/ml) and T_{max} (0.25 h) were predicted from the convolution method. The plasma concentration-time profile is shown in Fig. 8. The results suggest that the pastilles could release

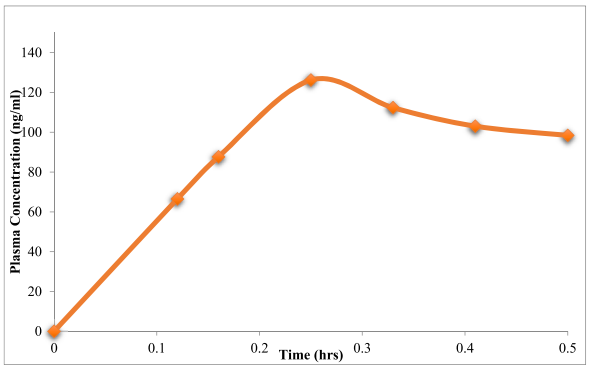

Fig. 8. Predicted plasma concentration-time profile.

the drug immediately, as it has a short onset of action. Hence, this convolution method is beneficial for designing and selecting formulations prior to *in-vivo* studies in humans and animals.

3.10. Stability

An accelerated Stability study was performed per ICH guidelines for six months at 40 ± 2 °C and 75 ± 5 % RH. The pastilles were removed at pre-determined intervals and assessed for their physical properties and drug-related parameters. There was no significant change in physical properties, drug content, or drug release patterns.

3.11. BATA model

Statistical data were obtained using one-way ANOVA analysis with Post hoc Tukey's test employing graph pad prism 6.01. According to the experimental procedure, the rats were permitted to drink simple distilled water, pure drug solution, pastille solution, and marketed tablet solution at the fixed time point, and licking frequency was calculated concerning water. Water's licking frequency was considered 100 %, while 50 % inhibition in licking frequency indicates the awful taste of medicament. The rat showed that a marketed formulation has 88 lick numbers, while with pastilles, it was 81 lick numbers (Fig. 9). These results suggest no significant difference in licking behavior for the marketed and pastilles solutions. The taste of the marketed formulation was good. The licking frequency above 80 indicates that taste masking is effective and bitter taste is completely masked. Here, one-way ANOVA and Post hoc Tukey's test were applied to compare the observed data. At the same time, the p-value of marketed and pastille formulations was found to be > 0.05, indicating the value is statistically insignificant. Thus, it concludes that the taste of pastilles and the marketed formulation exhibit comparable licking frequency, which may be acceptable by human volunteers. A comparison of TDL, pastilles, Marketed tablets of TDL, and Simple distilled water was carried out using Prism software, as shown in Table 8.

3.12. Comparison of TDL pastille with marketed formulation

The newly developed pastilles of TDL were compared with the marketed formulation in terms of disintegration time, dissolution profile, and other qualitative parameters. The disintegration time of the optimized formulation is 5 ± 0.1 min, whereas, for the marketed formulation, it was 11 ± 0.3 min. TDL pastilles could release more than 90 % of drug release in 15 min while 55 min in the case of the marketed formulation. In addition, the time and cost required for pastille formulation are significantly less due to fewer steps and excipients. Tablet manufacturing requires organic solvent in the wet granulation method and dust generation during the mixing, shifting, and compression stages. There is no use of organic solvent in the manufacturing of pastille formulation and no dust generation. A newer eco-friendly industrial oral solid dosage form approach was developed in this context.

4. Conclusion

Immediate-release TDL pastilles were successfully formulated, integrating a qualitative risk assessment and QbD approach. Polyox N-10 and Kyron T-314 were found to be promising excipients for the designing of pastilles. The amount of PEG 4000, Polyox N 10, and Kyron T-314 significantly influenced the chosen critical quality attributes. The single-step modified method formulated pastilles and achieved the desired solubility and dissolution of the TDL. The BATA model confirmed taste masking and observed a newer alternative

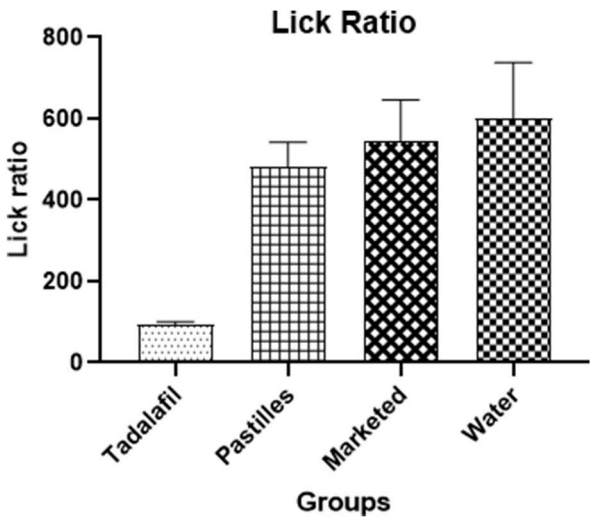

Fig. 9. Lick ratio.

Table 8
Comparison by Tukey's multiple comparisons tests.

Tukey's multiple comparison tests	Mean Diff.	95 % CI of diff.	Significant?	Summary	P value
TDL vs. Pastilles	−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

approach to identifying taste masking to the other preclinical trials. The newer eco-friendly approach was explored in the industry. The novel unexplored formulation may be helpful to the industry due to the fact that it does not use organic solvents, there is no dust generation, and it has a single-step manufacturing process. The pastilles will be explored as an alternate dosage form to a tablet at the commercial level due to its abundant benefits.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The *in-vivo* animal study was conducted, and approval was taken from the Institutional Animal Ethics Committee of Anand Pharmacy College. (Protocol Number: APC/2021-IAEC/2101)

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CRediT authorship contribution statement

Hardik Rana: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Meghna Panchal:** Methodology, Investigation, Formal analysis, Data curation. **Vaishali Thakkar:** Writing – review & editing, Software, Resources, Project administration, Conceptualization. **Tejal Gandhi:** Software, Project administration, Funding acquisition. **Mansi Dholakia:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors do not have any declarations of interest.

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List of abbreviation

FTIR	Fourier transforms infrared spectroscopy
DSC	Differential scanning calorimetry
TDL	TDL
QbD	Quality by design
BATA	Brief Access Taste Aversion
QTPP	Quality Target Product Profile
CQAs	Critical quality attributes
ED	Erectile dysfunction
PDE-5	Phosphodiesterase type 5

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