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Enhancing manufacturing efficiency with notch-enabled tooling: Cost-effective osmotically controlled release tablets using metformin HCl

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ABSTRACT

Laser drilling is commonly used in the production of osmotic-controlled release tablets but is expensive and time-consuming. An alternative is using customized tooling to compress the tablet blend and create the required orifice, which can reduce costs and improve efficiency. This study presents a cost-effective approach using a specially designed notch-enabled tool to replace laser drilling in osmotic tablet manufacturing. A 21 × 10 mm oval-shaped tool with a 0.7 mm notch and tapered dies was designed using S7 material to assess feasibility. Metformin hydrochloride (HCl) osmotic tablets were formulated using controlled notch tooling, eliminating the laser drilling step. Core composition, coating materials, and coating parameters were optimized via full factorial design. The formulation was refined by adjusting the ratios of povidone K29/30 and sodium lauryl sulfate, while the coating used 15% polyethylene glycol with a 90:10 acetone-to-water ratio. The coating process was optimized with specific spray rates and bed temperatures. Tablet evaluation included parameters such as bulk density, disintegration time, hardness, friability, and *in vitro* dissolution. This approach led to the efficient manufacturing of Metformin HCl extended-release tablets, improving swallowability and minimizing weight gain, without the need for laser drilling. This notch-enabled tooling method shows significant potential for industrial-scale production.

INTRODUCTION

Current global pharmaceutical industry-based research is basically focused on developing new drugs with cost effectiveness having better drug delivery systems for patient compliance and effective therapeutic potential. Conventional drug delivery formulations do not have the capabilities to control drug release profiles for maintaining the appropriate concentration of drug at site-specific regions for the desired time [1,2]. Advancement of technology in the development of long and sustained drug release profile dosage forms has been improved in countless ways due to intense and vigorous research in this field to improve the physical and biopharmaceutical limitations of numerous drugs [3,4].

An osmotic controlled-release tablet is an advanced controlled-release system that has a semipermeable outer membrane with a laser-drilled small orifice that allows fluid to enter *via* osmosis through a semipermeable membrane [5]. The osmosis phenomenon causes osmotic pressure which is responsible for API release through the drilled small orifice opening. The coating provides protection against gastric fluids and prevents drug irritation-related issues such as ulceration, nausea, and vomiting [6]. Irrespective of dosage, the coating also provides limited release of drug through the polymer semipermeable membrane to impart a prolonged release profile of API [7,8].

Metformin hydrochloride (HCl) is a globally accepted drug for the treatment of type 2 diabetes mellitus having high solubility *via* a prototypical transport-mediated mechanism [9]. Metformin HCl acts by inhibiting the absorption of intestinal glucose in addition improves peripheral glucose uptake and lowers fasting plasma insulin which results in a reduction of blood glucose concentrations. It has been reported that

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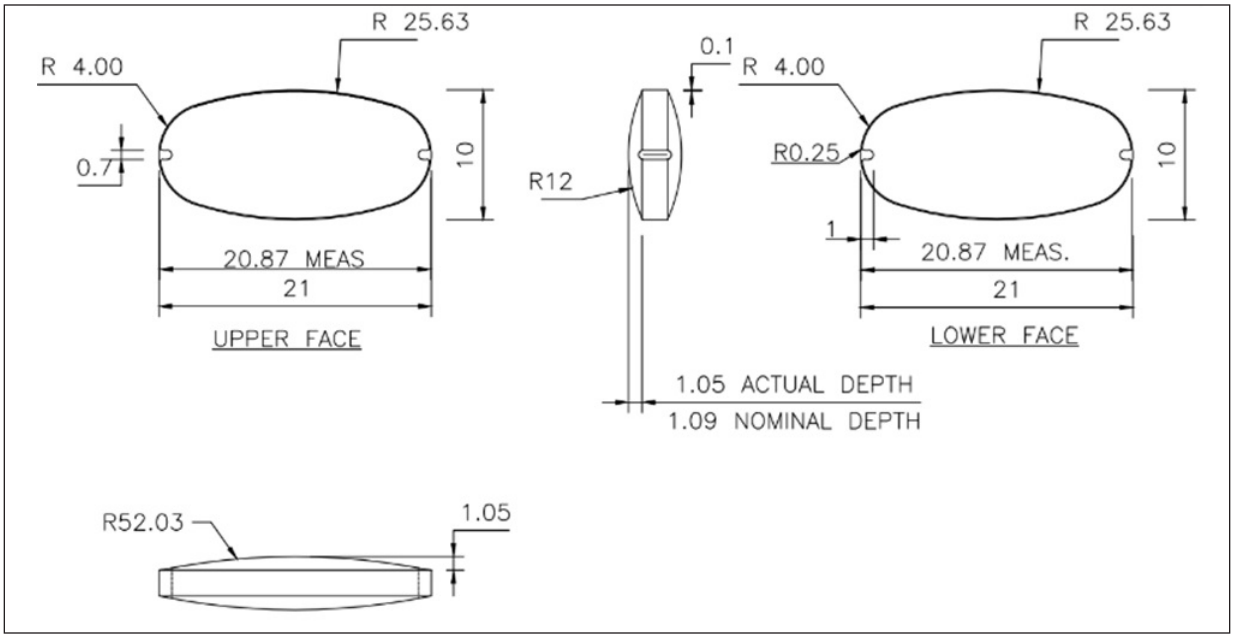


Figure 1. Design parameters of special notch tooling for metformin osmotic system.

gastrointestinal intolerance restricts its use in some subjects but its extended-release formulation can provide improved gastro intestinal tolerability and reduce dosing frequency [10,11].

In 1974, a US patent (3845770) osmotic tablet was made using laser drilling after a semi-permeable coating. Due to sophisticated laser drilling steps, the costs of production of these tablets are too high which increases treatment costs [12,13]. Drilling holes without the laser has been tried earlier but the reproducibility and accuracy of orifice within parameters could not be achieved. On the other side, the sophisticated process of laser step tablet production is costlier and time consuming. Customized tooling is another approach for developing osmotic tablets without the use of a drill [14].

With the above background, an effort was made to explore an alternative method for producing osmotic tablets without the requirement of drilling, using customized tooling. It was planned to validate the prepared tooling through established parameters and thereafter prepare an optimized formulation using metformin HCl as a suitable candidate.

The plan of the work was to develop tooling with an innovative notch in the die to create an *in situ* passageway for a cost-effective osmotic controlled drug delivery system, eliminating the requirement for laser drilling. In addition, the study aimed to optimize the composition of the core tablet, coating composition, and coating process parameters for osmotically controlled metformin HCl tablets.

MATERIAL AND METHODS

Materials

Metformin HCl was obtained as a gift sample from Sun Pharmaceutical Industries Limited, compression tooling purchased from Pacific Tools Pvt. Ltd., povidone (PVP) and sodium lauryl sulfate (SLS) sourced from BASF Pharma, hydroxypropyl methylcellulose, and cellulose acetate sourced from Dupont, magnesium stearate sourced from Peter Greven, polyethylene glycol (PEG) 400 sourced from Croda, acetone sourced from Thermo Fischer, and Gluconorm sustained release (SR) tablets (1 g) sourced from Lupin. Software JMP version 17 is used for the design of experiment data analysis.

Table 1. Composition of the tablet excipients and coating material.

	Ingredients	wt.(mg)	wt. (%)
	Core tablet		
	Metformin HCl	1,000	87.0
	PVP K 29/32	78	6.8
	SLS	56	4.9
	Purified water	qs	Qs
	Magnesium stearate	16	1.4
A	Total core tablet weight	1,150	100.0
	Coating solution	Ratio	
B	Cellulose acetate: PEG 400	60:40	10 parts
	Solvent: Acetone - water ratio	95:05	90 Parts

Development of tooling

Design of special notch tooling for the development of metformin osmotic tablets was done with dimensions as shown in Figure 1. Two tooling samples were manufactured with different notch widths of 0.7 and 0.9 mm with 1.0 mm depth of notch, with dimensions of 21 × 10 mm, an oval shape, tapered dies, and hard chrome plating using S7 MOC. One tool with an 11 mm width, round shape, 0.5 mm notch width, and 1.0 mm notch depth was manufactured with the same material of construction. Core tablets were prepared using composition as per Table 1 and evaluated for physical attributes.

Table 2. Formulation variables and response for osmotic controlled release system with notch.

Factors	Type	Low level (−1)	Middle level (0)	High level (+)	Response:
SLS level (mg/tab)	Continuous	45	55	65	Y1: Blend B.D.
Binder level (mg/tablet)	Continuous	60	80	100	Y2: Tablet Hardness
Type of binder	Categorical	HMPC E5 (Level 1)		PVP K29/32 (Level 2)	

Reservoir system controlled release tablets

Tablets without a special notch were prepared as per the formula (Table 1) to compare the performance of a notched osmotic system. The required quantities of PVP and SLS were dissolved in water. Sifting of the metformin was done using #36 BSS to ensure a uniform particle size and to break down any large agglomerates. Granulation was done using a solution of PVP and SLS in a fluid bed processor. After granulation, the wet mass was dried at 60°C. Subsequently, the dried granules were milled through a 0.8 mm sieve to ensure uniformity. To improve the tablet compression process, the in-process blend was lubricated with magnesium stearate, reducing friction between particles during compression. The blend was then compressed using plain 21 × 10 mm oval-shaped punches, shaping the granules into tablets. In preparation for coating, a coating solution with a 10% solid content was formulated. The tablets were spray-coated in a coating pan using this prepared coating solution. Finally, samples were collected at intervals of 5%, 10%, and 15% weight build-up. Since Metformin HCl extended release is independent of the pH of the media, hence Metformin HCl ER tablets dissolution was performed with 900 ml, pH 6.8 phosphate buffer, USP type-I/IP type –II (basket # 10) at 50 rpm.

Osmotic system with notch-controlled release tablets

Tablets with a special notch were optimized using a full factorial design to compare the performance of a notched osmotic system. Characterization of the developed tablet was carried out by evaluating blend bulk density, tablet disintegration time, tablet hardness (kp), sticking/picking, and friability. The formulation variables affecting responses with their ranges and their type are tabulated in Table 2. Experimental Run Matrix represents levels of each factor to prepare tablets with a special notch osmotic system to optimize core tablet composition, keeping magnesium stearate constant with ten batches using a full factorial design, as shown in Table 3. A similar manufacturing process as described in "Reservoir system-controlled release tablets" using specialized oval-shaped punches measuring 21 × 10 mm, featuring a notch-enabled design, was used. The tablets were spray-coated in a coating pan using a coating solution of cellulose acetate and PEG 400 with a 90:10 ratio of acetone and water (in a 95:5 ratio) as a solvent. Samples were collected to assess 2% and 3% weight build-up during the coating process.

Optimization of coating composition

After selection and optimization of the core tablet excipients, coating composition was optimized using full factorial design as shown in Table 4, and the design matrix for six trials is given in Table 5. This involved dissolving PEG in water and cellulose acetate in acetone separately. Subsequently, the PEG solution was carefully added to the cellulose acetate under constant stirring, maintaining this stirring for a duration of 45 minutes. The tablet coating process involved spray coating within a coating pan, utilizing a semi-permeable coating solution. Samples were collected at two different stages,

Table 3. Design matrix of tablets with special notch osmotic system.

S. No.	SLS level (mg/tablet)	Binder level (mg/tablet)	Type of binder
1	65 (+)	100 (+)	HMPC E5 (Level 1)
2	65 (+)	100 (+)	PVP K29/32 (Level 2)
3	65 (+)	60 (-)	PVP K29/32 (Level 2)
4	65 (+)	60 (-)	HMPC E5 (Level 1)
5	45 (−)	100 (+)	PVP K29/32 (Level 2)
6	45 (−)	100 (+)	HMPC E5 (Level 1)
7	55 (0)	80 (0)	HMPC E5 (Level 1)
8	55 (0)	80 (0)	PVP K29/32 (Level 2)
9	45 (−)	60 (−)	PVP K29/32 (Level 2)
10	45 (−)	60 (−)	HMPC E5 (Level 1)

Table 4. Factors and levels for coating composition of osmotic system with notch-controlled release.

Factors	Type	Low level	Middle level	High level	Responses:
% PEG in coating	Continuous	10	15	20	Dissolution in pH 6.8 PB
% Water in acetone	Continuous	5	10	15	

Table 5. Design matrix of tablet coating composition with special notch osmotic system.

S. No.	% PEG in coating	% Water in acetone	Response (Y) = *In vitro* dissolution in pH 6.8 PB
1.	10	15	
2.	20	5	
3.	10	5	
4.	15	10	
5.	15	10	
6.	20	15	

specifically when achieving 2% and 3% weight buildup on the optimized core tablet. Then, the *in vitro* dissolution profile was evaluated in pH 6.8 phosphate buffer, and drug release kinetics were evaluated using the zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Optimization of coating process

The selected and optimized composition of coating and tablet core was used for optimizing the coating process using full factorial design in ten trials by evaluating bed temp (˚C), spray rate (g/min), and curing time (minutes) as factors of the coating process on *in vitro* dissolution are given in Tables 6 and 7.

Characterization

Characterization of blend

Bulk Density of Blend (B.D.)

100 g of blend transferred into measuring cylinder of 250 ml; volume of sample noted (V0). Bulk density (g/cc) calculated using the formula [15]:

Bulk density (BD) =100 / V0.

Table 6. Factors affecting coating process of osmotic system with notch-controlled release.

Factors	Type	Low level	Middle level	High level	Responses: Dissolution in pH 6.8 PB
Bed temperature, °C	Continuous	24	28	32	
Spray rate (g/min)	Continuous	4	6	8	
Drying time (minutes)	Continuous	10	15	25	

Table 7. Design matrix of tablet coating process with special notch osmotic system.

S. No.	Bed temp (°C)	Spray rate (g/ minute)	Curing time (minutes)
1	32	8	5
2	24	4	25
3	32	8	25
4	28	6	15
5	24	8	25
6	28	6	15
7	24	8	5
8	32	4	5
9	32	4	25
10	24	4	5

Characterization of core and coated tablets

Tablet friability (%)

10 core tablets were weighed and placed in a rotating drum. The drum is rotated to 100 revolutions. The sample is reweighed after 100 revolutions to find % weight loss [16].

Tablet hardness (kp)

10 core tablets were placed under a hardness tester and the average was calculated [16].

Dissolution

One coated tablet was placed in each dissolution vessel (N = 12 units), USP type I (basket # 10 mesh) containing 900 ml pH 6.8 phosphate buffer, with 50 rpm basket rotation, 10 ml samples were withdrawn at regular time intervals with replacement of media. The sample is further diluted to 100 times. Absorbance was calculated in a UV spectrophotometer at 232 nm wavelength and the concentration of metformin HCl was estimated against a standard known solution of known concentration [17].

Disintegration time (mins)

Each core tablet was placed in 6 tubes of the basket in a disintegration apparatus with water as a medium, maintained at 37°C ± 2°C. Time in minutes noted for complete disintegration of tablets [18].

Drug release kinetics and similarity factor

The optimized batch and marketed product (Gluconorm SR 1 g tablets) were further analyzed to check drug release kinetics and the best-fit release model using zero order (% drug release= Slope × time), first order (log [Fraction unreleased] = Slope × time/2.303), Higuchi model (% Drug release = Slope × $[time]^{0.5}$), and Korsmeyer–Peppas equation (% Drug release = Slope × $[time]^{n}$). Similarity factor (f2) for dissolution profiles was calculated between the optimized batch and the marketed product on 12 units [7].

Stability studies

Stability studies were performed according to ICH guidelines. Tablets were packed in HDPE bottle 30's Count and charged on accelerated (40°C/75%RH/6 months) and long-term conditions (25°C/60%RH/6 months). The dissolution profile, F2 (similarity factor), and appearance of tablets were compared for initial and at 6 months stability [16].

Table 8. % Metformin release in 900 ml, pH 6.8 PB, 50 rpm (reservoir system).

% Cumulative drug Release (mean)										
Batch –KS1	**Time (hours)>>**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**
Sample -1	5% coat	27	49	80	95	100	104	…..	…..	…..
Sample -2	10% coat	5	22	53	72	88	96	100	102	103
Sample -3	15% coat	3	14	42	65	83	95	99	101	103

RESULT AND DISCUSSION

Tooling optimization

Core tablets with oval tooling (20 × 10 mm) having a notch width of 0.9 and 1.0 mm notch depth show friability of 0.9% w/w, and chipping was observed at notch edges, hence not considered for further trials. This may be due to a wide notch. Core tablets with round tooling (11 mm width) having a notch diameter of 0.5 with 1.0 mm notch depth produced friction noise between punches and the tablet surface while ejecting tablets, hence not considered for further trials. Core tablets with oval tooling (20 × 10 mm) having a notch width of 0.7 with 1.0 mm notch depth show friability of 0.3% w/w without any noise while tablet ejection from the machine. Hence, this tool was finalized for further trials.

Table 9. Characterization of blend BD and core tablet hardness.

Batch No.	Blend BD (g/cc)	Tablet hardness (kp)
CORE1	0.54	18.2
CORE2	0.53	20.2
CORE3	0.59	13.1
CORE4	0.62	12.9
CORE5	0.48	22.5
CORE6	0.62	18.6
CORE7	0.55	13.6
CORE8	0.52	17
CORE9	0.47	12.1
CORE10	0.59	11.3

For reservoir systems

Osmotic tablets with 5% coating weight build up were able to control the release of the drug till 6 hours only; however, with 10% and 15% coat, drug release can be controlled till 12 hours as shown in Table 8. One tablet out of 6 tablets after completion of dissolution found pin holes at the edges causing leakage in the system. The reason for the leakage was the insufficient mechanical strength of the coating membrane, leading to the formation of pinholes in the coating. Also, as a result of 10% and 15% weight gain during the coating process, the total tablet weight increased.

For notch-controlled osmotic tablets optimization

Characterization of blend and core tablet

The bulk density of the blend was found in a range of 0.48–0.92 g/cc; Core tablet hardness ranges from 11.3 to 16.3 kp, (Table 9). Tablet DT was found between 5 minutes 50 seconds to 9 minutes 10 seconds for all trials. Batch no. CORE4 observed the sticking of tablets, no picking/sticking was observed in other experiments.

Regression analysis for core tablet

In response blend BD (g/cc), *p* value for the blend BD model was 0.0169 (<0.05) and R^2 = 0.98, hence model was significant which is shown in Table 10. The type of binder was significant with *p* value of 0.0068; however, SLS level and binder level had no impact on blend BD. All two-factor interactions are significant given in Table 11. Pareto chart, surface profiler, and prediction profiler are shown in Figure 2A, 2C, and 2E for response: Blend BD. In response

Table 10. ANOVA summary for regression.

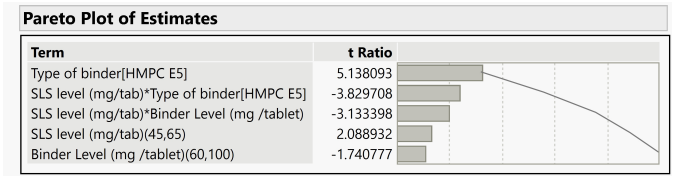
S. No.	Response	Source of variation	Degree of freedom	Sum of squares	Mean square	*F* ratio	*p* value
1	Blend B.D.	Model	5	0.02404000	0.004808	11.6558	**0.0169**
		Error	4	0.00165000	0.000412		
		C. Total	9	0.02569000			
		Model R^2			0.98		
2	Hardness of core tablet	Model	6	131.15525	21.8592	27.4412	**0.0102**
		Error	3	2.38975	0.7966		
		C. Total	9	133.54500			
		Model R^2			0.98		

p value < 0.05 suggest significance.

Table 11. Parameters estimated for response blend BD (g/cc).

Term	Estimate	Std rrror	*t* Ratio	Prob > |*t*|
Intercept	0.5185	0.049255	10.53	0.0005*
SLS level (mg/tablet)	0.0015	0.000718	2.09	0.1050
Binder level (mg/tablet)	−0.000625	0.000359	−1.74	0.1567
(SLS level (mg/tablet)-55)*(Binder level (mg /tablet)-80)	−0.000112	0.000036	−3.13	0.0351*
Type of binder [HMPC E5]	0.033	0.006423	5.14	0.0068*
(SLS level (mg/tablet)-55)*Type of binder [HMPC E5]	−0.00275	0.000718	−3.83	0.0186*

**p* value < 0.05 suggest significant term.



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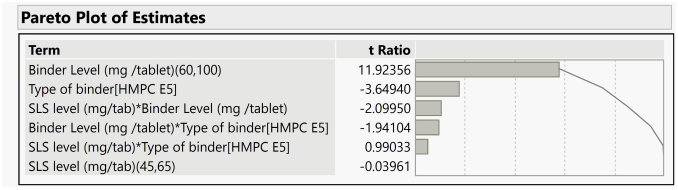

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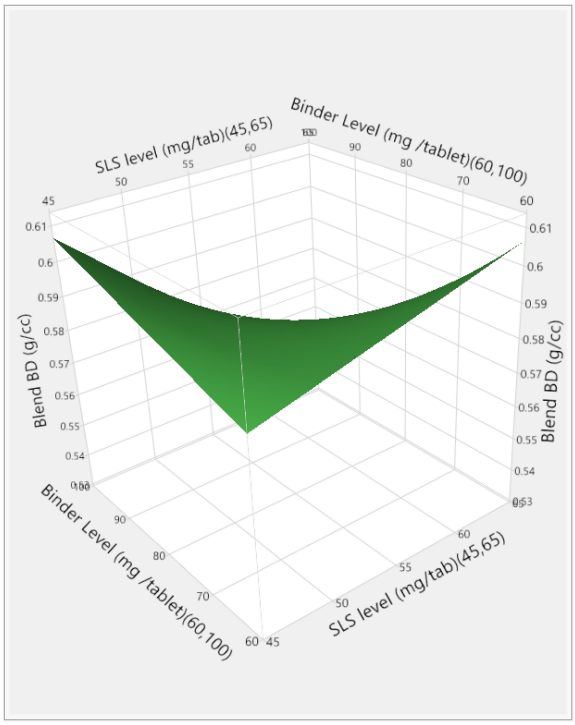

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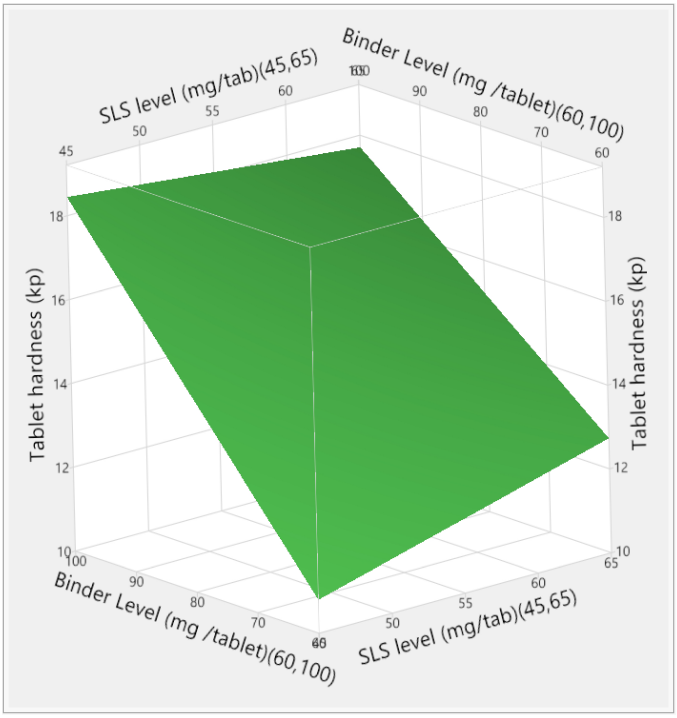

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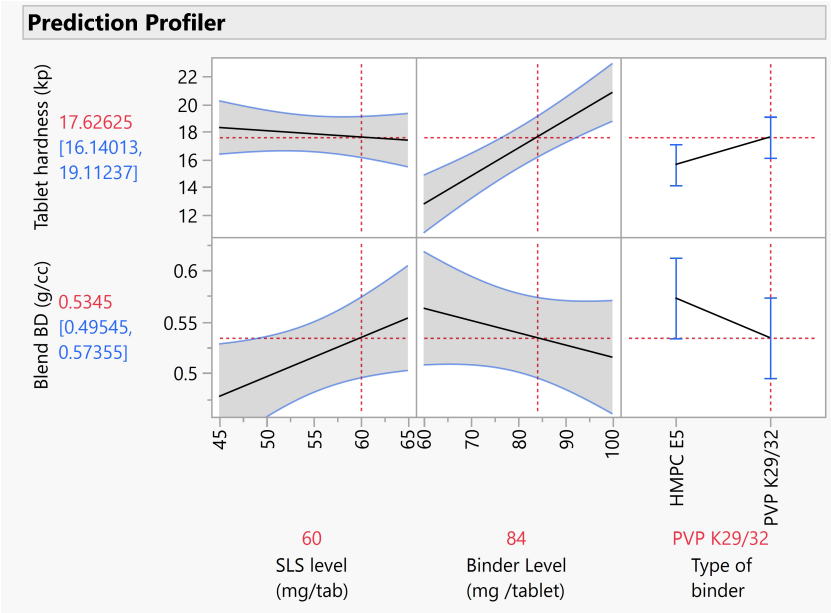
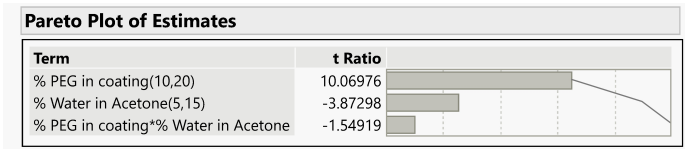


(e)

Figure 2. (a) Pareto chart for response- blend BD (g/cc). (b) Pareto plot of response tablet hardness (kp). (c). Surface profiler for response -blend B.D. (d) Surface profiler for response hardness of tablets. (e) Prediction profiler for response.



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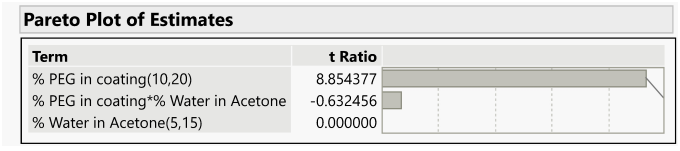

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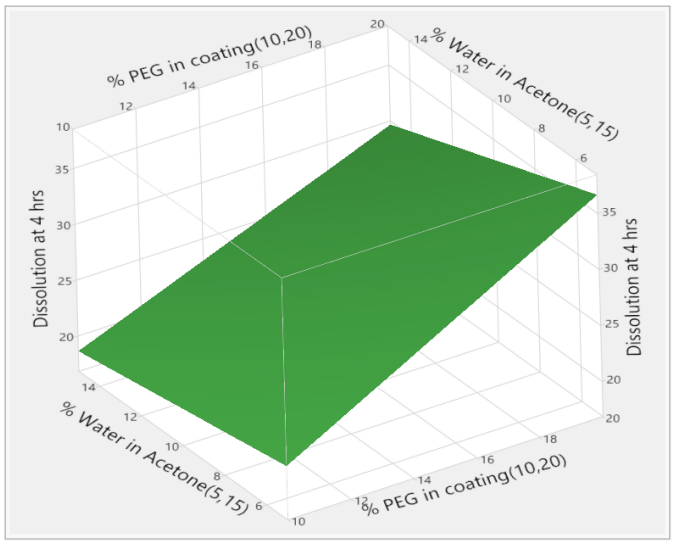

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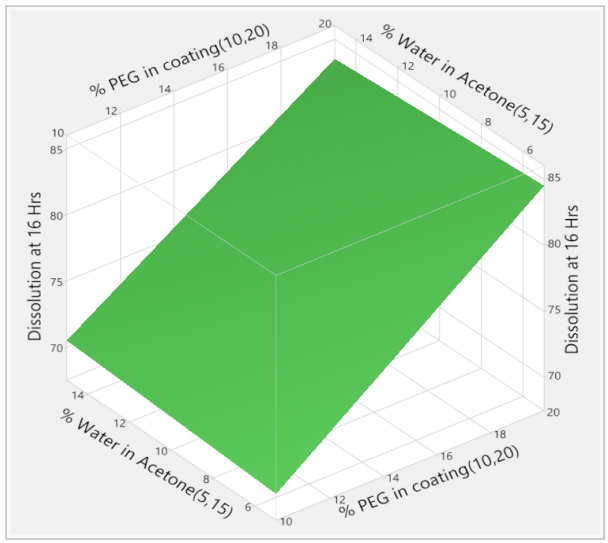

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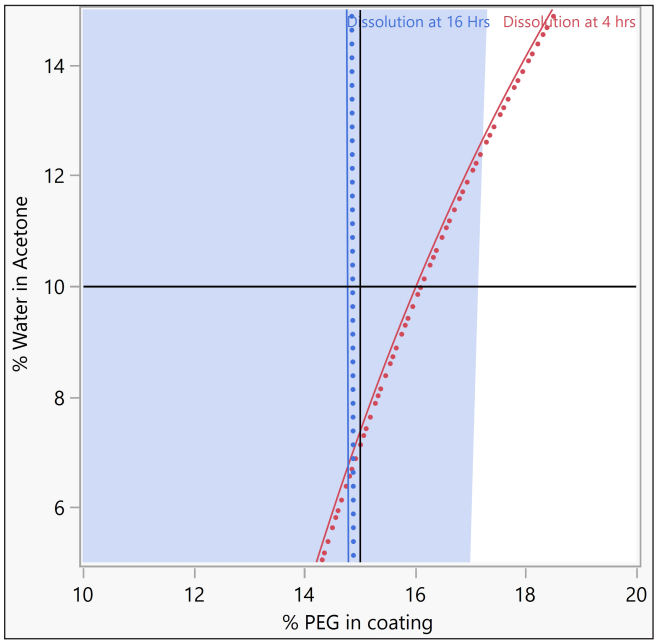


(e)

Figure 3. (a) Pareto chart for dissolution at 4 hours. (b) Pareto chart for dissolution at 16 hours. (c) Surface profiler for dissolution at 4 hours. (d) Surface profiler for dissolution at 16 hours. (e) Contour profiler for dissolution at 4 and 16 hours.

to tablet hardness (kp), the *p*-value was 0.0102 (<0.05) and R^2 = 0.98; hence, the model was significant which is Shown in Table 10. Binder level and type of binder were significant with *p* value of 0.0013 and 0.0355, respectively (Table 12). Based on the Pareto chart, prediction profiler, and surface profiler as shown in 2B, 2D, and 2E, increasing the binder level will increase the hardness of core tablets. On the physical description, batches with HMPC E5 at low levels

show a capping phenomenon, which may create concerns in the coating process, hence PVP K29/32 was selected as a binder with 84 mg/tablet, and SLS at 60 mg/tablet was finalized for further trails.

Characterization for coating composition

The characterization of the percentage of PEG and percentage of water in acetone were studied and the impact on *in vitro* dissolution data are shown in Table 13 with different coating compositions.

Regression analysis for coating composition

From ANOVA Table 14, *p*-value and R^2 value of the model were 0.0247 (<0.05) and 0.98, respectively, for dissolution at 4 hours. *p*-value and R^2 value of the model were 0.0369 (<0.05) and 0.98, respectively, for dissolution at 16 hours, and hence both models were significant as shown in Table 14. *p*-value for lack of fit was 0.564 (>0.05) and 0.4359 (>0.05) for 4 and 16 hours dissolution models respectively which suggest insignificant lack of fit. % PEG in the coating was a significant factor in dissolution at 4 and 16 hours. (*p* value

Table 12. Parameters estimated for response tablet hardness (kp).

Term	Estimate	Std error	*t* Ratio	Prob > |*t*|
Intercept	0.96875	2.164464	0.45	0.6848
SLS level (mg/tablet)	-0.00125	0.031555	-0.04	0.9709
Binder level (mg /tablet)	0.188125	0.015778	11.92	0.0013*
(SLS level (mg/tablet)-55)*(Binder level (mg /tablet)-80)	-0.003313	0.001578	-2.10	0.1266
Type of binder [HMPC E5]	-1.03	0.282238	-3.65	0.0355*
(SLS level (mg/tablet)-55)*Type of binder [HMPC E5]	0.03125	0.031555	0.99	0.3950
(Binder level (mg /tablet)-80)*Type of binder [HMPC E5]	-0.030625	0.015778	-1.94	0.1476

*p value < 0.05 suggest significant term.

Table 13. *In vitro*-dissolution data of metformin HCl in pH 6.8 phosphate buffer for analysis of coating composition with 2% weight build up and drug release kinetics.

Batch no>		Coat-1	Coat-2	Coat-3	Coat-4	Coat-5	Coat-6
% PEG in coating		10	20	10	15	15	20
% Water in acetone		15	5	5	10	10	15
In vitro % Drug release (in pH 6.8 PB), $n = 6$	1 hour	7	8	5	6	4	10
	2 hours	8	22	9	11	13	25
	4 hours	19	37	22	25	27	30
	6 hours	30	47	33	37	36	49
	8 hours	39	58	40	47	49	61
	12 hours	54	70	53	59	58	68
	16 hours	70	84	69	79	77	83
	20 hours	82	95	84	88	89	94
	24 hours	96	95	95	94	94	96
Zero order	R^2	0.99	0.95	0.99	0.99	0.97	0.93
	K	4.39	5.90	4.32	4.89	4.79	5.78
First order	R^2	0.98	0.99	0.99	0.97	0.98	0.97
	K	−0.07	−0.10	−0.07	−0.09	−0.09	−0.10
Higuchi	R^2	0.93	0.97	0.95	0.95	0.95	0.96
	K	18.05	21.75	18.01	20.43	20.14	21.37
Korsmeyer-Peppas	R^2	0.97	0.96	0.99	0.99	0.96	0.95
	K	5.70	9.95	5.13	6.19	5.32	11.68
	n	0.90	0.85	0.97	0.94	1.02	0.76

Table 14. ANOVA summary for regression (Coating composition optimization).

S. No.	Response	Source of variation	Degree of freedom	Sum of squares	Mean square	*F* ratio	*p* value
1	Dissolution at 4 hours	Model	3	198.00000	66.0000	39.6	**0.0247**
		Error	2	3.33333	1.6667		
		C. Total	5	201.33333			
		Model R^2			0.98		
				Lack of fit (*p* value)			**0.5641**
2	Dissolution at 16 hours	Model	3	197.00000	65.6667	26.27	**0.0369**
		Error	2	5.00000	2.5000		
		C. Total	5	202.00000			
		Model R^2			0.98		
				Lack of fit (*p* value)			**0.4359**

p value < 0.05 suggest significance.

Table 15. Parameters estimated for response tablet coating composition dissolution at 4 hours.

Term	Estimate	Std error	t *ratio*	Prob > |*t*|
Intercept	12.166667	2.386304	5.10	0.0364*
% PEG in coating	1.3	0.129099	10.07	0.0097*
% Water in acetone	−0.5	0.129099	−3.87	0.0607
(% PEG in coating-15)*(% Water in acetone-10)	−0.04	0.02582	−1.55	0.2615

**p* value < 0.05 suggest significant term.

Table 16. Parameters estimated for response tablet coating composition dissolution at 16 hours.

Term	Estimate	Std error	t ratio	Prob > |*t*|
Intercept	56	2.922613	19.16	0.0027*
% PEG in coating	1.4	0.158114	8.85	0.0125*
% Water in acetone	0	0.158114	0.00	1.0000
(% PEG in coating-15) *(% Water in acetone-10)	−0.02	0.031623	−0.63	0.5918

**p* value < 0.05 suggest significant term.

< 0.05). On increasing the % PEG in the coating membrane, dissolution was increased as per Tables 15 and 16. Based on the Pareto chart, surface profiler, and contour profiler (Fig. 3a–e), % PEG was significantly affecting drug release. Hence, % PEG at 15%w/w and water: acetone ratio of 10:90 are to be selected for further studies. *In vitro* dissolution data fitted in zero order, first order, Higuchi and Korsmeyer–Peppas model for all 6 trials with varying PEG levels and water/acetone ratio. R^2 for zero order ranges 0.93–0.99 suggests model fitting. R^2 for the first order and Higuchi model also >0.9. Release exponent (n) from Korsmeyer–Peppas equation for all batches suggests anomalous (non-fickian) transport as the value of n lies between $0.45 < n < 1.0$ except one batch number Coat-5 with PEG and water/acetone ratio at a center point which suggest super Case-II transport (Table 13).

Characterization for the coating process

In the characterization of the coating process various parameters involved bed temp., Spray rate, curing time with their different values, and dissolution data are shown in Table 17.

Regression analysis for coating process

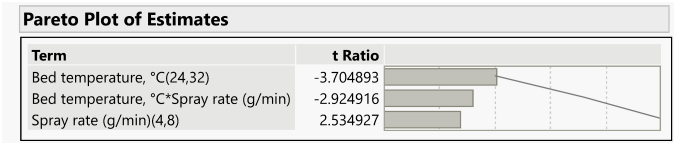
From ANOVA Table 18, *p*-value and R^2 value of the model were 0.0105 (<0.05) and 0.83, respectively, for dissolution at 4 hours. *p*-value and R^2 value of the model were 0.0103 (<0.05) and 0.83, respectively, for dissolution at 16 hours. *p*-value for lack of fit was 0.1499 (>0.05) and 0.4585 (>0.05) for 4 and 16 hours dissolution models respectively which suggest an insignificant lack of fit. Bed temperature and spray rate are significantly impacting dissolution at 4 and 16 hours (*p* value < 0.05). The quadratic term between factors is also significant with *p* value < 0.05. Increasing the spray rate increases dissolution at 4 and 16 hours while increasing bed temperature reduces the dissolution at 4 and 16 hours as shown in Tables 19 and 20, respectively. Based on the Pareto chart, contour profiler, and surface profiler, spray rate of 6–8 g/min, curing time of 15 minutes, and temperature of 26°C–32°C for the coating process proposed as an optimum range (Fig. 4a–e).

Release kinetics and similarity factor for optimized batch (CP-4) and marketed product

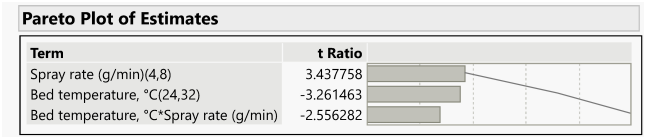
In vitro dissolution data for optimized formulation (CP-4) and marketed product Gluconorm SR 1g tablets fitted with zero order, first order, Higuchi and Korsmeyer–Peppas model. R^2 for zero order >0.9 suggests model fitting. R^2 for Higuchi model also >0.9. Release exponent (n) from the Korsmeyer–Peppas equation for both products suggests super case II transport as a value of $n > 1.0$ (Table 21). A similarity factor was found F2 = 54 between optimized and marketed formulations (Table 21).

Stability studies

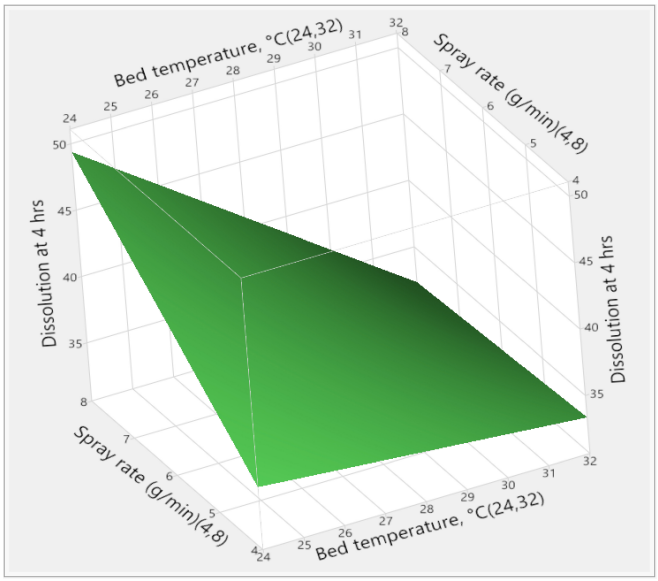
There was no change in the appearance and dissolution profiles of the optimized batch after 6 months at accelerated and



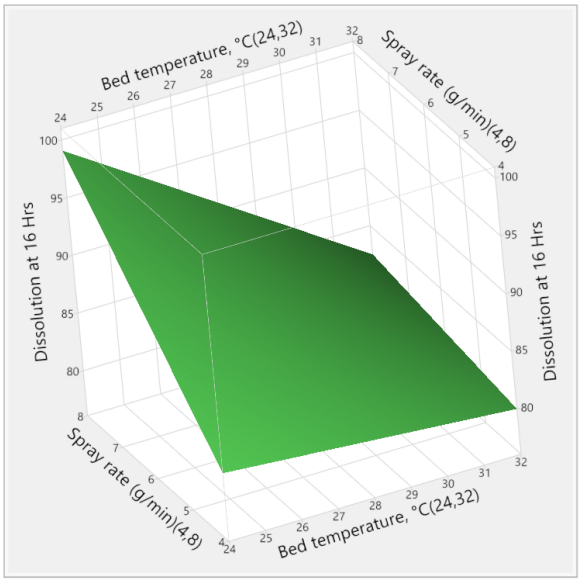
(a)



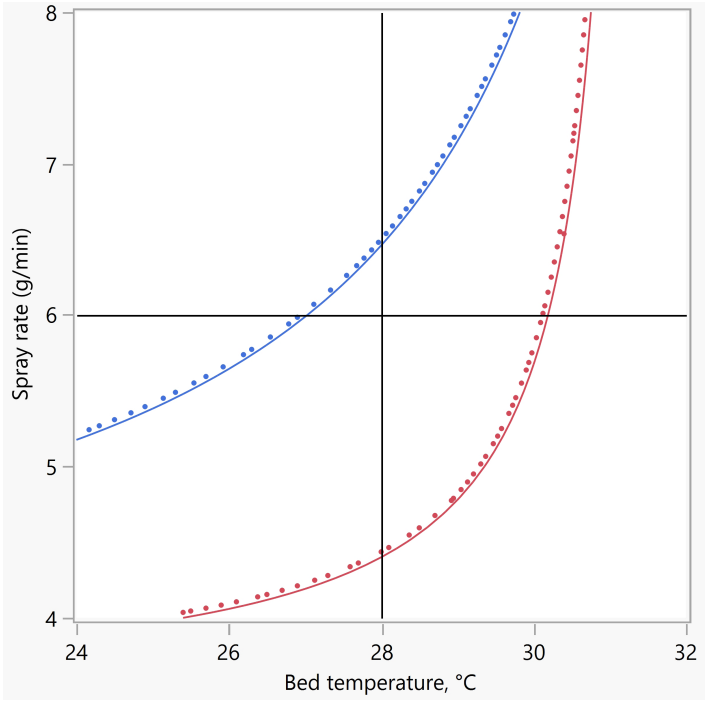
(b)



(c)



(d)



(e)

Figure 4. (a) Pareto chart for dissolution at 4 hours. (b) Pareto chart for dissolution at 16 hours. (c) Surface profiler for dissolution at 4 hours. (d) Surface profiler for dissolution at 16 hours. (e) Contour profiler for dissolution at 4 hours and 16 hours.

long-term conditions from initial samples. F2 values between the initial (0 month) and 6 months dissolution profile were 75 (>50) and 72 (>50), at ACC and LT conditions respectively which suggest similar profiles during stability.

Table 17. Dissolution data of metformin HCl in pH 6.8 phosphate buffer for analysis of coating process with 2% weight build up.

Batch No.	Bed temp (˚C)	Spray rate (g/minute)	Curing time (minutes)	Dissolution (in pH 6.8 PB)								
				1 hour	2 hours	4 hours.	6 hours	8 hours	12 hours	16 hours	20 hours	24 hours
CP-1	32	8	5	4	13	30	39	54	63	78	89	94
CP-2	24	4	25	4	12	36	37	54	60	84	86	95
CP-3	32	8	25	6	15	33	40	55	65	86	90	95
CP-4	28	6	15	4	13	41	48	52	58	88	92	96
CP-5	24	8	25	12	28	49	58	70	82	99	99	99
CP-6	28	6	15	3	11	41	46	50	59	88	93	96
CP-7	24	8	5	11	26	48	58	71	82	98	99	99
CP-8	32	4	5	8	15	37	48	63	72	84	90	96
CP-9	32	4	25	7	18	28	47	61	70	75	81	95
CP-10	24	4	5	4	10	33	36	53	60	79	84	93

Table 18. ANOVA summary for regression (Coating process optimization).

S. No	Response	Source of variation	Degree of freedom	Sum of squares	Mean square	*F* ratio	*p* value
1	Dissolution at 4 hours	Model	3	377.50000	125.833	9.5691	**0.0105**
		Error	6	78.90000	13.150		
		C. Total	9	456.40000			
		Model R^2			0.83		
		Lack of fit (*p* value)					**0.1499**
2	Dissolution at 16 hours	Model	3	466.37500	155.458	9.6633	**0.0103**
		Error	6	96.52500	16.088		
		C. Total	9	562.90000			
		Model R^2			0.83		
		Lack of fit (*p* value)					**0.4585**

p value < 0.05 suggest significance.

Table 19. Parameters estimated for response tablet coating process for *in vitro* dissolution at 4 hours.

Term	Estimate	Std error	*t* ratio	Prob > |*t*|
Intercept	61.1	9.8312	6.21	0.0008*
Bed temp (˚C)	−1.1875	0.320522	−3.70	0.0100*
Spray rate (g/min)	1.625	0.641044	2.53	0.0444*
(Bed temp (˚C)-28)*(Spray rate (g/min)-6)	−0.46875	0.160261	−2.92	0.0265*

**p* value < 0.05 suggest significant term.

Table 20. Parameters estimated for response tablet coating process for dissolution at 16 hours.

Term	Estimate	Std error	*t* ratio	Prob > |*t*|
Intercept	103.65	10.87397	9.53	<.0001*
Bed temp (˚C)	−1.15625	0.354519	−3.26	0.0172*
Spray rate (g/minute)	2.4375	0.709038	3.44	0.0138*
(Bed temp (˚C)-28)*(Spray rate (g/minute)-6)	−0.453125	0.177259	−2.56	0.0431*

**p* value < 0.05 suggest significant term.

Table 21. *In vitro*-dissolution data and drug release kinetics for optimized formulation vs marketed product.

	Time	Optimized Formulation (CP-4)	Marketed Product (Gluconorm SR 1g tablets)
In vitro % drug release (in pH 6.8 PB), $n = 12$	1 hour	4 (0.8)	7 (1.0)
	2 hours	13 (0.7)	17 (2.1)
	4 hours	41 (3.1)	33 (2.5)
	6 hours	48 (4.7)	53 (5.1)
	8 hours	52 (4.7)	62 (3.6)
	12 hours	58 (2.9)	71 (2.6)
	16 hours	88 (2.6)	93 (2.2)
	20 hours	92 (2.9)	96 (2.5)
	24 hours	96 (3.0)	98 (2.9)
Zero order	R^2	0.92	0.99
	K	5.16	8.11
First order	R^2	0.89	0.99
	K	-0.12	-0.13
Higuchi	R^2	0.93	0.92
	K	22.12	23.28
Korsmeyer-Peppas	R^2	0.92	0.99
	K	5.81	7.50
	n	1.04	1.06
Release Mechanism		Super case II transport	Super case II transport
F2 (Similarity factor)		54	

DISCUSSION

Osmotic systems utilize osmotic pressure to release drug substances from the dosage form. The osmotic systems for dosage form come in existence in 1974, and since then many modifications have been made to improve this drug delivery system. The current osmotic drug delivery system utilizes a laser drilling process to make orifice in tablets which makes process costlier and time consuming. Alternate to laser drilling reservoir systems are also available in the market which involve coating with water-soluble pore former which generally increases the volume of tablets, especially in the case of high-dose drugs like Metformin HCl. To make the process efficient and cost-effective osmotically controlled delivery without laser drilling and without high volume (%) coating novel tool was developed. The current study successfully developed a tool design incorporating notches, and different depths, and widths of notches were evaluated utilizing oval-shaped modified punches. Punches measuring 21 × 10 mm with notch sizes of 0.7 mm and a depth of 1.0 mm were finalized for further optimization of dosage forms. The optimization focused on the extended-release osmotic composition of Metformin HCl. Binder level,, SLS level and type of binder (PVP and HMPC) studied using full factorial design resulting in an optimal combination of 84 mg/tablet of PVP K29/30 and 60 mg/tablet of SLS. Furthermore, the coating composition was fine-tuned, % PEG in coating and acetone to water ratio were studied using full factorial design leading to a finalized formulation consisting of 15% PEG in the coating membrane, employing an acetone to water ratio of 90:10. Refinements were also made to the coating process, spray rate, curing time, and bed temperature studied using full factorial design which provides optimized spray rate of 6–8 g/min, curing time 15 minutes, and a bed temperature range of 26°C–32°C. Optimized formulation shows zero order drug release kinetics and similarity established with marketed product. These optimization efforts significantly contribute to the efficient manufacturing of Metformin HCl extended-release tablets, characterized by improved swallowability, and minimized weight gain without the use of laser drilling processing step. This novel tooling approach proved effective in the production of Metformin HCl tablets, which are typically larger due to their high dosage, while achieving reduced weight gain compared to the traditional reservoir system. However, there is a need for a few modifications/ advancements by compression machine manufacturers for such type of novel tooling to optimize the impact of force on tooling by machine rollers, and improvement of lubrication mechanism in machine, which can be explored by machine manufacturers.

CONCLUSION

In the current research, substituting laser drilling with specialized notched tools can make drug production cheaper and create tablets with reduced tablet volume. Composition and process variables optimized for tablet dissolution. Compression machine manufacturers are encouraged to explore integrating these specialized tools into their machines to capitalize on these advancements. Going ahead, collaboration between pharmaceutical manufacturers, tool manufacturers, and compression machine manufacturers will be crucial to further refine and implement these technologies. This collaborative effort can drive innovation in drug delivery systems, paving the way for more efficient and affordable osmotic tablet dosage forms globally. As the field continues to evolve, integrating notched tools into compression machines stands out as a pivotal advancement for the pharmaceutical industry.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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