

# Application of Factorial Design in the Premixing Operation of Diltiazem Timed-Release Pellets

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## Kumaravelrajan *et al.*: Factorial Design for Timed-Release Pellets

The purpose of this study was to prepare diltiazem timed-release pellets using non pareil seeds. An important step in the preparation of timed-release multiparticulate dosage forms was to mix a pilot mixture composed of various polymers or waxes with different concentration. By using the three-factor and two-level factorial design for the pilot mixing process, the mixing can be distinguished technically than the trial and error method. Core, non pareil seeds prepared by using a sugar solution. A fluidized bed processor was used to coat diltiazem on to the non pareil seeds. Hydroxypropyl methylcellulose E15 was used as coatings for non pareil seeds, with various percentage (10 %, 20 % and 30 %) in two levels (16.66 % and 33.33 %). According to the design matrix, pilot mixing was carried out for *in vitro* dissolution studies and optimized batches were prepared for masterblend and mixture based on the results. The Pareto chart supported the analysis of variance results for the model simplification and eliminating non-significant terms ( $p > 0.05$ ). The optimal process variable selected for optimizing the diltiazem timed-release pellets formulation was set to be pilot mix I=24.9 %, pilot mix II=16.6 % and pilot mix III=16.6 %. The optimized formula showed that half-life period was  $2.361 \pm 0.243$  h and shelf-life period was 6.875 h.

**Key words:** Quality by design, diltiazem, palletization, factorial design, timed-release

Modified-release preparations can be administered orally in single or multiple-unit dosage forms. Single-unit formulations contain the active ingredient within the single tablet or capsule, where as multiple-unit dosage forms comprise of number of discrete particles that are combined into one dosage unit. They may exist as pellets, granules, sugar seeds (non pareil) and minitables<sup>[1]</sup>. Multi-Unit Pellet System (MUPS) is one of the most popular Multi-Unit Dosage Form (MUDF) because of its unique advantages in physical properties (e.g., spherical shape) and mechanical properties (e.g., elastic and deformation ability and tensile strength)<sup>[2,3]</sup>. Pellet formulations were better at producing sustained release effects and reducing variability in blood levels, it was claimed that a pellet formulation had shorter gastric emptying times and longer total intestinal residence times than tablets<sup>[4,5]</sup>. Non Pareil Seeds (NPS) can be prepared by conventional and fluid-bed process<sup>[6,7]</sup>. Quality by Design (QbD) is formally defined as “a systematic approach for product development that begins with predefined objectives and emphasizes product and process understanding and process control,

based on sound science and quality risk management<sup>[7,8]</sup>. QbD is now seen as a key enabler for achieving the desired performance of developed formulation. Screening designs (full-factorial, Plackett–Burman designs and mixture designs) are used to indicate the most important of all factors, potentially influencing the formulation, product or process. Response surface designs (central-composite design, Box–Behnken design and Doehlert design) are again applied to find the optimal factor settings and mixture designs to optimize, for instance, the excipients composition in formulations<sup>[9,10]</sup>. Conventional pharmaceutical development procedures are based on quality by testing and have become out of use. In these methods, product quality was assured by controlling raw materials (i.e. drugs and excipients) and manufacturing techniques<sup>[11]</sup>.

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The challenges in the production of a timed-release dosage form to the manufacturing industry are pilot mixing of different level of the coated pellets by trial and error until satisfactory results obtained. This can be overcome by QbD approach<sup>[12]</sup>. The identification of Critical Process Parameters (CPPs) becomes a part of production process parameters and finally the risk assessment of the drug substance attributes to the development of the product<sup>[13,14]</sup>. Taking antihypertensive drugs at night can significantly reduce Morning Blood Pressure Fluctuations (MBPS), thereby improving blood pressure variability<sup>[15]</sup>. Diltiazem Hydrochloride (HCl) has a short biological half-life and high dosing frequency (usually three to four times a day), making it a potential candidate for the development of Sustained-Release (SR) formulations<sup>[16]</sup>. Diltiazem pellets prepared by Fluid-bed coating process reported to be ideal for the preparation of controlled-release formulations<sup>[17]</sup>. The purpose of this study was to prepare diltiazem timed-release pellets using NPS. An important step in the preparation of timed-release multiparticulate dosage forms is to mix a pilot mixture composed of various polymers or waxes with different concentration. By using the 2<sup>3</sup> factorial design for the pilot mixing process, the mixing can be distinguished technically than the trial and error method. Core, NPS prepared by using sugar solution. A fluidized bed processor was used to coat diltiazem to the NPS. Hydroxypropyl methylcellulose (HPMC) E15 used as NPS coating polymer. According to the design matrix, pilot mixing was carried out for *in vitro* dissolution studies and optimized batches were prepared for master blend and mixture based on the results. The three-factor and two-level (2<sup>3</sup>) factorial design was used to optimize the Diltiazem NPS (DNPS) pilot mix. Hence, the amount of hydrophilic polymers coated with DNPS namely, amount of HPMC K15-10 %, HPMC K15-20 % and HPMC K15-30 % as the prime selected independent variables (factors), which were varied at two levels (low 16.66 %) and 33.33 % high) for pilot mixing operation. 50 % drug released (t<sub>50</sub>) and 90 % drug release (t<sub>90</sub>) were chosen as a dependent variable to test the release property of DNPS. Various studies have been conducted on the optimized mixture, such as Entrapment Efficiency (EE) and surface morphology.

## MATERIALS AND METHODS

### Materials:

Diltiazem HCl was purchased from Divi's Laboratories Limited, Hyderabad. Hydroxypropyl Cellulose (HPC-

M-FP-300) was procured from Aualon, Gujarat. HPMC 15 cps E15-LV (12-15) obtained from Colorcon Asia Pvt. Ltd., Singapore. Polyvinyl pyrrolidone (PVP K30, 5.5-8.5) was purchased from Nanchang Industrial Holding Group Co. Ltd. and Feicheng Rui Tai Fine Chemicals, China. Triethyl citrate (C12-35.2) was purchased from Zhonglan Industry Co.Ltd, China. All other chemicals purchased for manufacturing and quality control as an analytical grade.

### Methods:

**Thermal analysis:** Thermograms of unplasticized and plasticized polymeric films were obtained by using a Differential Scanning Calorimetry (DSC) (Mettler Toledo DSC2A-00837, Mumbai, India) and STAR<sup>®</sup> software (Mettler Toledo, Giessen, Germany) to determine the melting point or the glass Transition (T<sub>g</sub>) temperature (n=2–3). The temperature calibration was completed with the melting transition of indium. The sample (7–10 mg, stored in a vacuum desiccator prior to analysis) was sealed in an aluminium tank and placed in the NETZSCH DSC. The scanning rate was 10°/min over a temperature range of 50°–300°. All tests were run under a nitrogen atmosphere.

**Formulation development:** Diltiazem 120 mg timed release pellets were prepared. At first, preliminary experiments were conducted to prepare NPS with a syrup base, but after a long fluidized bed dryer coating process, particles with the desired shape were formed. Hence, combining 3 % PVP with the syrup solution resulted in a satisfactory particle size. Another method of developing DNPS is to use a traditional coating pan, but the drug loading effect is poor, so the coating pan method is abandoned. Diltiazem and HPC (7 % w/v) polymers are separately dissolved in water and mixed. Water was used as the granulating fluid, sufficient to prepare a wet blend that is suitable for extrusion. The prepared aqueous suspension was sprayed on to the NPS. The third stage of development is HPMC polymer coating, which carried out through a conventional coating pan to form pellets of sufficient thickness. For coating, the most common cellulose-based polymer used for sustained release dosage forms is a HPMC because, HPMC is known as a pellets-hardening agent and also reported as a pore-forming agent in pellets manufacturing. Plasticizers are other components incorporated into polymer coatings to enhance film-forming properties, because most polymers become brittle at room temperature. The commonly used plasticizer for particle coating is 10 % w/w triethyl citrate.

**Preparation of NPS:** The pellets were prepared in a fluid-bed granulator (WSG-Pro, Pam Glatt, Thane, India) using the wet granulation technique (Table 1A). 1 kg of pharma grade sugar and 5 % starch passed to a 60 mesh sieve, was used at first<sup>[18]</sup>. This powder mixture was loaded into the product chamber of the machine. After a fluidization for 3 min, a pre-weighed amount of syrup approximately 300 ml was sprayed through an atomizing nozzle (1.2 mm diameter) into the powder at a rate of 30 ml/min with the aid of a peristaltic pump. The process continued for an hour until pellets developed a 0.4 mm thickness in size. Later pellets passed through 30 mesh, but retained in the 50 mesh used further coating process. The inlet air temperature was kept constant at 45°±1° and the process airflow at 0.3-0.5 bar. Once all the syrup was sprayed, the pellets were dried for 15 min at 450°.

**Preparation of DNPS:** The core consists of diltiazem, which was coated on the NPS using HPC as a binder (Table 1B). HPC was dissolved in purified water at a ratio of 1:0.0028 (drug-polymer)<sup>[19]</sup>. Using the conditions previously described, the drug was suspended in the binder solution and sprayed onto the sugar spheres (NPS) in a fluidized bed processor. Binder weight divided by drug weight was 0.028. Core composition was calculated as 1 kg of the drug in 1000 g of NPS (1:1) basis and drug content was expressed as fractional content (Fc, the weight of the drug in the cores/total weight of the cores×100 %=250×1245×100 =20.08 %). Spray efficiency of the drug layering process was reported as the actual weight gain divided by the

theoretical weight gain expressed as percentage. Cores were sieved to remove undersized material and agglomerates before coating.

**Coating of polymer with DNPS:** The polymer membrane consisted of a HPMC (Table 1C) were prepared as three variables of the coating solution HPMC 10 %, 20 % and 30 %. The triethyl citrate (10 % w/v) was used as plasticizer and talc as anti-static material. Coating polymers and plasticizer were dissolved in isopropyl alcohol and methylene chloride at 1:1 ratio. Talc was suspended in the coating solution at 10 % of the weight of dissolved solids as an anti-tack agent. The suspension was sprayed onto the DNPS of traditional coating pan (316 stainless steel size 18"×12", RPM 0-28, temperature 30°-65°).

#### Pilot mixing of pellets:

**Experimental design:** A 2<sup>3</sup> factorial design was used to optimize the diltiazem HCl pellets pilot mix operation. Before performing the dissolution study of diltiazem pellets *in vitro*, a factorial design of 2<sup>3</sup> was applied to all trial batches (F1-F8) of pilot mixtures, as shown in Table 2. The pilot mix was prepared by mixing of diltiazem coated pellets of three different polymer coat 10 %, 20 % and 30 % HPMC E15, at higher (33.33 %) and lower (16.66 %) level with or without dummy pellets to make 100 % according to design matrix. Hence, every batch consisted of either a lower or higher level of HPMC coated diltiazem core. These pellets (DNPS) were mixed after the determination of their drug content. The t<sub>90</sub> and t<sub>50</sub> are studied as dependent variables (responses). Design-Expert 11.0.6.1 software (Stat-Ease Inc., USA) was used for generation and evaluation of the statistical experimental design.

$$Y = b_0 + b_1A + b_2B + b_3C + b_4AB + b_5AC + b_6BC \quad \text{Eqn (1)}$$

Where Y is the dependent variable and b<sub>0</sub> is the intercept; b<sub>1</sub>, b<sub>2</sub>, b<sub>3</sub>, b<sub>4</sub>, b<sub>5</sub> and b<sub>6</sub> are regression coefficients; A, B and C are independent variables and AB, AC and BC are the interactions between variables. One-way Analysis of Variance (ANOVA) was applied to estimate the significance of the model (p<0.05) and individual response parameters.

#### Evaluation of diltiazem pellets:

**Pellet size analysis:** Using a combination of vertical movements (sieve numbers 10, 14, 16 and 18), diltiazem HCl pellets were analyzed through a series of successively decreasing sieve vibrations<sup>[20]</sup>. The pellets in motion finally oriented to the screen (sieve 16) with

**TABLE 1: COMPOSITION OF NPS, PREPARATION AND COATING OF DILTIAZEM PELLETS**

Preparation of NPS: Ingredients	(g)
Pharma grade sugar*	1000
Starch	50.0
Povidone	30.0
Sugar syrup	qs
Purified water	qs
<b>Preparation of DNPS**</b>	
Diltiazem HCl	1000
Hydroxy propyl cellulose	28.0
Purified water	qs
<b>Formulation of polymer coating with DNPS</b>	
HPMC	1.5-2.5
Triethyl citrate	1.0
Talc	0.0125
Isopropyl Alcohol	50.0
Methylene Chloride	50.0

Note: \*formula for 1 kg of NPS and \*\*formula for 1 kg of diltiazem pellets

**TABLE 2: DESIGN MATRIX FOR PILOT MIX WITH RESPONSES**

Batch	A: Pilot mix I <sup>a</sup> (HPMC-10) %	B: Pilot mix II <sup>b</sup> (HPMC-20) %	C: Pilot mix III <sup>b</sup> (HPMC-30) %	Dummy pellets (%)	Total pilot mix (%)	t <sub>50</sub> (h)*	t <sub>90</sub> (h)**
F1	16.66 (-1)	16.66 (-1)	16.66 (-1)	50.02	100	0.756	4.629
F2	33.33 (+1)	16.66 (-1)	16.66 (-1)	33.35	100	1.2089	5.31
F3	16.66 (-1)	33.36 (+1)	16.66 (-1)	33.35	100	1.2476	5.999
F4	33.33 (+1)	33.33 (+1)	16.66 (-1)	16.68	100	1.973	6.26
F5	16.66 (-1)	16.66 (-1)	33.33 (+1)	33.35	100	2.222	6.48
F6	33.33 (+1)	16.66 (-1)	33.33 (+1)	16.68	100	2.789	6.98
F7	16.66 (-1)	33.3 (+1)	33.33 (+1)	16.68	100	3.062	7.30
F8	33.33 (+1)	33.33 (+1)	33.33 (+1)	0.01	100	4.197	7.50

Note: A, B and C represent the main effects (factors); (+1): Higher level (33.3 %) and (-1): Lower level (16.6 %), \*t<sub>50</sub> (h) (%): The time required to release 50 % of the drug. Response variable I, value of mean±standard deviation, n=3, \*\*t<sub>90</sub> (h) (%): The time required to release 90 % of the drug. Response variable II, value of mean±standard deviation, n=3, <sup>a</sup>content of pilot mix I, both level used to mix 100 % pellets and <sup>b</sup>content of pilot mix II and pilot mix III, was higher level (+1) used to mix 100 % pellets

its smallest two sizes, opens and passes through the screen with the next smaller nominal opening (sieve 18). Upon completion of the sieving process, the weight of the sieves was measured and compared to the weight of the sieves before the addition of the sample. Through the addition of the mass fraction on each sieve, from the smallest to the largest sieve, the cumulative mass distribution of the test sample was calculated.

**EE:** The prepared pellets were evaluated for the percentage of drug loading and drug EE<sup>[21]</sup>. The pellets were crushed well and a powder equivalent to 100 mg dissolved in 100 ml of methanol and filtered through a 0.45 µm cellulose acetate membrane filter, 5 ml of aliquot was withdrawn. The drug loading was determined by Ultraviolet (UV) detection at 236 nm and the percentage (%) drug release and EE was calculated using the following equations:

$$EE \% = \frac{\text{Drug added} - \text{Free untrapped drug}}{\text{Drug added}} \times 100$$

**Theoretical Polymer Coat Weight (TPCW):** TPCW is defined as the weight of dissolved solids<sup>7</sup> applied (including plasticizer) divided by the sum of core and applied dissolved solids weights. During this process, the sample was removed from the coating pan to ensure that the TPCW passes improved, through the sample port without interrupting the spraying process. Drug content was reported as fractional content (Fc, weight of drug in total pellet weight) or potency (Fc×100 %). Samples were sieved to remove undersize material and agglomerates before image analysis.

**In vitro dissolution study:** Drug release tests were carried out using a dissolution tester. The dissolution tester was calibrated using salicylic acid by United States Pharmacopeia (USP) dissolution calibrator. Test samples containing 120 mg of diltiazem HCl pellets

was placed in a USP dissolution apparatus II containing 900 ml of distilled water at 37° (paddle method at 100 rpm). Diltiazem HCl belongs to the BCS class I drug (high solubility and high permeability). Drug release and absorption do not depend on the pH value of gastrointestinal tract. Therefore, distilled water is used as the dissolution medium<sup>[22]</sup>. By comparing the UV scanning (200-400 nm) of different products with the UV scanning of pure drugs and was found that the detection method was not interfered by excipients at 236 nm. The USP XXIII rotating paddle method (VanKel 700, VK 650a, 37°, 900 ml, 0.1 M HCl, 0.1 M pH 7.4 phosphate buffer, 100 RPM, n=3) was used to study the release of drug from coated pellets. The samples (5.0 ml) were collected at 1, 2, 3, 4, 5, 6, 8 and 9 h intervals and analysed or stored in the refrigerator until analysis (within 24 h). Diltiazem content and release were detected, spectrophotometrically at 236 nm<sup>[23]</sup> (Electrolab, TDT-0P, India).

**Fitting kinetic model:** In order to analyze the drug release mechanism of these diltiazem timed release pellets, the *in vitro* dissolution data were fitted to various mathematical models, such as zero-order, first-order, Higuchi and Korsmeyer-Peppas models<sup>[24]</sup>.

#### Statistical analysis:

Statistical optimization was performed using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). All other data were analysed with simple statistics.

#### Scanning Electron Microscopy (SEM) study:

The external and surface morphology of diltiazem pellets were analyzed by SEM<sup>[25]</sup>. The pellets were fixed on supports with carbon-glue and coated with gold-palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Samples

were then observed with an FEI, Quanta 200 scanning electron microscope (FEI, Quanta 200 SEM, USA) at 20 kv.

## RESULTS AND DISCUSSION

In order to confirm the physical state of diltiazem HCl in the pellets, the DSC of Diltiazem HCl and the physical mixture of diltiazem HCl and polymer were measured. The DSC trace of diltiazem HCl showed a sharp endothermic peak at 186.23°, its melting point. The physical mixture of diltiazem HCl and polymers showed the same thermal behavior 171.31° as the individual component, indicating that there was no interaction between the diltiazem HCl and the polymer in the solid state. These suggest that the diltiazem HCl existed in an amorphous or disordered crystalline phase as a molecular dispersion in polymeric matrix. The size of the prepared diltiazem HCl pellets was measured using sieve diameter method and found to be between 0.761 and 0.882 mm. It was found that the trapping efficiency of experiment 1 was 77 %. The encapsulation efficiency was increased by 85 % in another trial batch by optimizing coating condition. This serves to calculate the equivalent value of diltiazem HCl in the pellets. The angle of repose, flow through an orifice, moisture content, bulk/tapped volume and density, compressibility index, and Hausner ratio were evaluated to determine the flow characteristics. The calculated angle of repose for the powder was 22.67°±0.4° to 27.24°±0.2° indicating that powder exhibits a fair flow. The inter-particle interaction that affects the performance of the powder body affects the powder flow. A comparison of the tapped and bulk densities is useful to give a measure of the relative importance of these interactions in powder. Such a comparison is often said as an index (the compressibility index or

the Hausner ratio) of the ability of the powder to flow. Estimated compressibility index and Hausner ratio for powder mixture were 1.99 %±0.06 % to 9.39 %±1.06 % and 1.022 %±0.03 % to 1.13 %±0.04 %, respectively. Friability values were 0.079 % to 0.096 %.

Table 2 lists the time required for all formulations to release 50 % and 90 % ( $t_{50}$  and  $t_{90}$  of the drug. The drug release from pilot-mix according to design matrix was largely depends on the coating level. Firstly,  $t_{50}$  of the drug was found to be 0.75 and 4.19 h for F1 (all three variable low level) and F8 (all high level) as level of pilot mix in coating increased, proportionately the drug was released from pellets irrespective of polymer concentration. Similarly, when comparing with high level coating for F4, F6 and F7, the  $t_{50}$  was found to be 1.97, 2.78 and 3.06 h. Although the coating thickness was increased to the greatest extent, when the HPMC concentration higher (F6, 2.78 h), the release of the polymer better due to the swelling and solubility of the polymer. On the other hand, when comparing  $t_{50}$  of F2, F3 and F5,  $t_{50}$  was 1.20, 1.24 and 2.22 h respectively. However,  $t_{50}$  for F3 slightly higher than other two formulations. This fact could be due to level and more ethyl cellulose present in coating membrane.

The time required for all formulations to release 90 % of the shown in fig. 1. In pilot mix F1 and F8, lower and higher  $t_{90}$  values are given for 4.6 and 7.5 h. Formulations 4, 6 and 7 composed of pilot mix II and pilot mix III largely, thickness showed a higher  $t_{90}$  of 6.2 h, 6.9 h and 7.3 h. Similarly, F2, F3 and F5 are released for 5.3 h, 5.9 h and 6.4 h, respectively. Because of small differences in the pilot mix I concentration, no significant change in the pattern of release between F3 and F5.

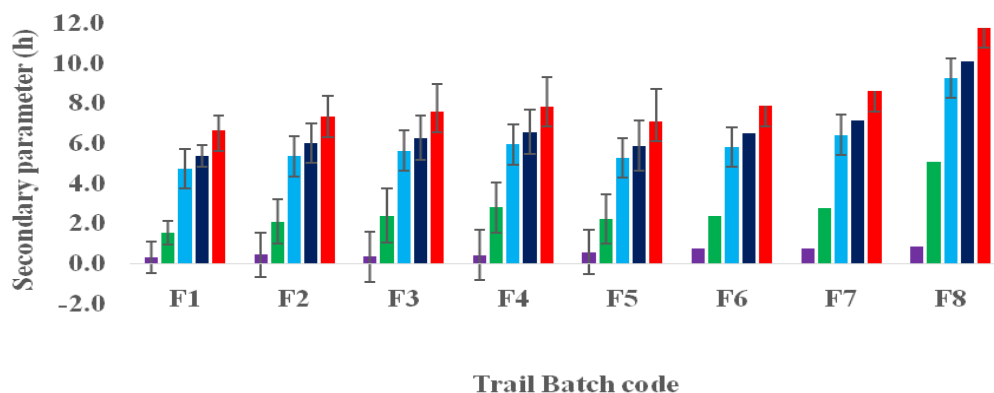


Fig. 1:  $T_x$  value of diltiazem hydrochloride pellets from trial batch (secondary parameters)

Note: (■)  $t_{25}$ , (■)  $t_{50}$ , (■)  $t_{75}$ , (■)  $t_{80}$  and (■)  $t_{90}$  is time in hours require to release drug from pellets, n=3; mean±standard deviation

Through  $2^3$  factorial designs, a total of 8 pilot mixtures of diltiazem HCl pellets were proposed for 3 independent variables HPMC 10 %, 20 %, 30 % coat as pilot mix I, II and III respectively. In the current study, the effects of these independent variables,  $t_{50}$  (h) and  $t_{90}$  (h) were studied as the optimal response parameters. The results of the ANOVA indicated that these models were significant for all response parameters as shown in Table 3. After fitting these data, Design-Expert 10.0.6.1 software provides suitable polynomial model equations including each main factor and interaction factor. The model simplified by eliminating the unimportant terms ( $p>0.05$ ) in the modeling equation obtained by the multiple regression analysis. The model equation with  $t_{50}$  (h) as the response becomes,

$$t_{50} = +2.1819375 + 0.3600375 \times A + 0.4379625 \times B + 0.8855625 \times C + 6.2 \times 10^{-3} AB + 9.4 \times 10^{-2} AC + 7.1.2 \times 10^{-3} BC, (R^2=0.9991; F \text{ value}=15.09; p<0.0076) \text{ Eqn. (2)}$$

The model equation relating with  $t_{90}$  (h) as the response becomes

$$t_{90} = +6.30725 + 0.20525 \times A + 0.4575 \times B + 0.75775 \times C + 5.50 \times 10^{-3} AB - 6.12 \times 10^{-3} AC - 5.02 \times 10^{-3} BC, (R^2=0.9994; F \text{ value}=45.40; p<0.0015) \text{ Eqn. (3)}$$

As shown in fig. 2A-fig. 2B, the statistical significance of each response coefficient was studied through the Pareto chart. These graphs describe the statistical significance of each response coefficient. Coefficients with t values of effects above the Bonferroni line are designated as significant coefficients with t values of effects between Bonferroni line and t limit line are termed as coefficients likely to be significant. Coefficients with t values of

effects below the t limit line are statistically insignificant coefficients. Therefore, these Pareto charts supported also the ANOVA results for the model simplification by eliminating non-significant terms ( $p>0.05$ ) in both the model equations<sup>[26]</sup>. A numerical optimization technique based on the desired method was adopted to realize a new optimized formula with the required response. The ideal range of these responses is limited to  $2 \text{ h} \leq t_{50} \leq 50 \%$  and  $7 \text{ h} \leq t_{90} \leq 90 \%$ , while the factor range is limited to  $20 \% \leq A \leq 25 \%$ ,  $15 \% \leq B \leq 20 \%$ ,  $15 \% \leq C \leq 20 \%$ . In order to evaluate the optimization capabilities of these models generated from the results of  $2^3$  factorial design, the optimal process variable selected for optimizing the diltiazem timed-release pellets formulation was set to be pilot mix I=24.9 %, pilot mix II=16.6 % and pilot mix III=16.6 %. Numerical analysis was performed to obtain the best value based on the expected response. Table 4 depicts the results (actual values) of predicted values obtained from the mathematical model and actually observed. The optimized formula shows that  $t_{50}$  is  $2.361 \pm 0.243$  h,  $t_{90}$  is 6.875 h and the error range is small ( $<10 \%$ ), indicating that the mathematical model obtained through  $2^3$  factorial designs is very suitable.

The three-dimensional response surface plot is very useful in learning about the main and interaction. The influence of independent variables (factors) and the two-dimensional contour map (fig. 3A-fig. 3D) is a visual representation of the response value. The three-dimensional response surface map and corresponding contour map related to  $t_{50}$  (h) and  $t_{90}$  (h) show that with the increase of HPMC concentration (20 % pilot II and 30% pilot mix III), the dead value of  $t_{50}$  and  $t_{90}$

**TABLE 3: PARAPHRASE OF ANOVA FOR RESPONSE PARAMETERS**

Source	Sum of squares	D.f	Mean square	F value	p value	
Model- $t_{50}$	7.81	2	3.9	15.09	0.0076	S
B-Pilot mix II (HPMC-20)	1.53	1	1.53	5.93	0.059	
C-Pilot mix III (HPMC-30)	6.27	1	6.27	24.25	0.0044	
Model- $t_{90}$	6.6	3	2.2	45.4	0.0015	S
A-Pilot mix I (HPMC-10)	0.337	1	0.337	6.95	0.0578	
B-Pilot mix II (HPMC-20)	1.67	1	1.67	34.53	0.0042	
C-Pilot mix III (HPMC-30)	4.59	1	4.59	94.73	0.0006	

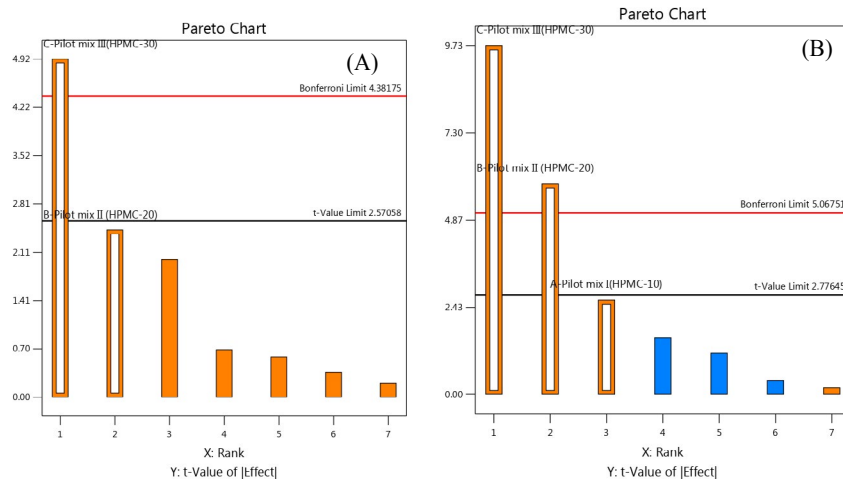
Note: D.f: Degree of freedom; A, B and C represent the main effects (factors) and S: Model Significant

**TABLE 4: DESIGN SPACE, ANALYSES FOR OPTIMIZATION**

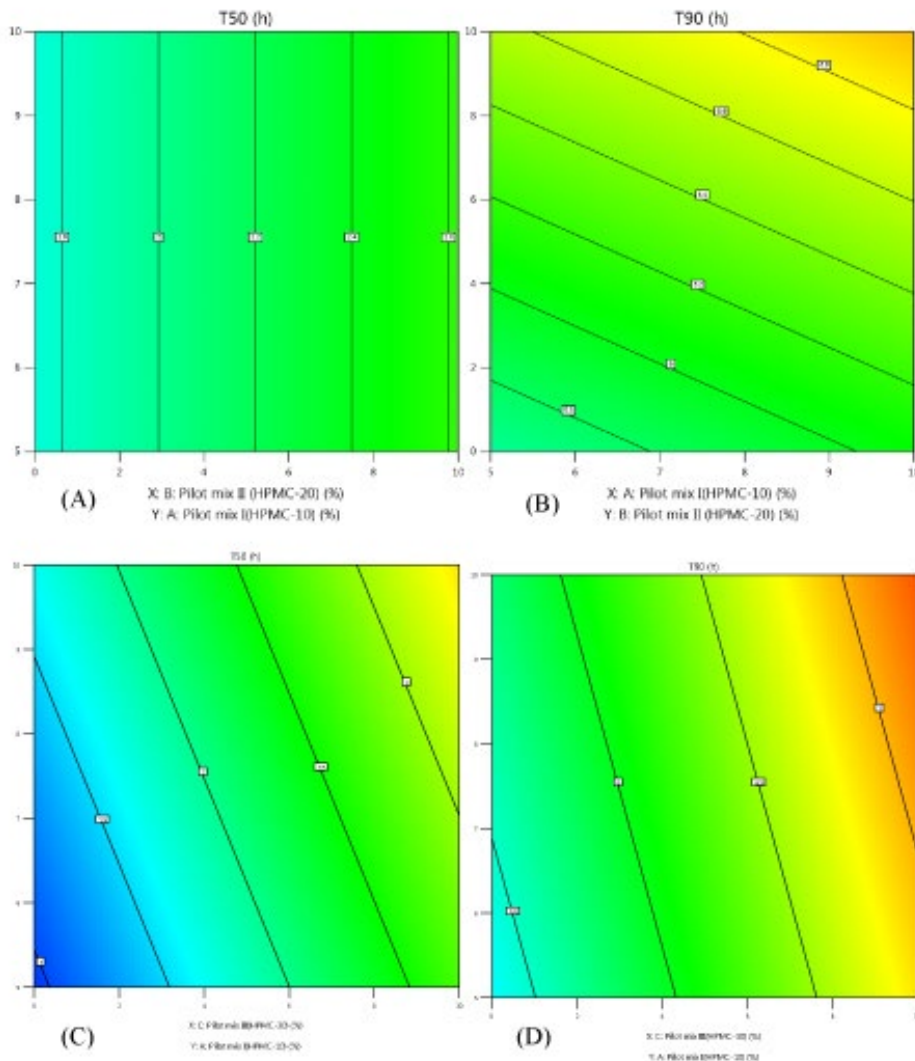
Factor	Name	Level (%)	Response	Predicted mean (h)	Observed* (h)
A	Pilot mix I (HPMC-10)	24.9	$t_{50}$	2.18194	2.361
B	Pilot mix II (HPMC-20)	16.6	$t_{90}$	6.30725	6.875
C	Pilot mix III (HPMC-30)	16.6	% error**	8.203	9.005

Note: \*Observed values=mean±standard deviation, n=3; \*\*Percent error=(Actual value-predicted value)/predicted value×100 and A, B and C represent the main effects (factors)

(fig. 4A-fig. 4B). The model found to be significant ( $p \leq 0.005$ ) indicating that the selected model described the relationship between the independent variable and the dependent variable well.



**Fig. 2:** Pareto chart relating, (A):  $t_{50}$  (h) and (B):  $t_{90}$  (h)  
 Note: (■) Positive effects and (■) Negative effects



**Fig. 3:** Effect of percentage of (A): Pilot mix I, pilot mix II on  $t_{50}$ ; (B):  $t_{90}$ ; (C): Pilot mix I, pilot mix III on  $t_{50}$  and (D)  $t_{90}$ , presented by contour plot

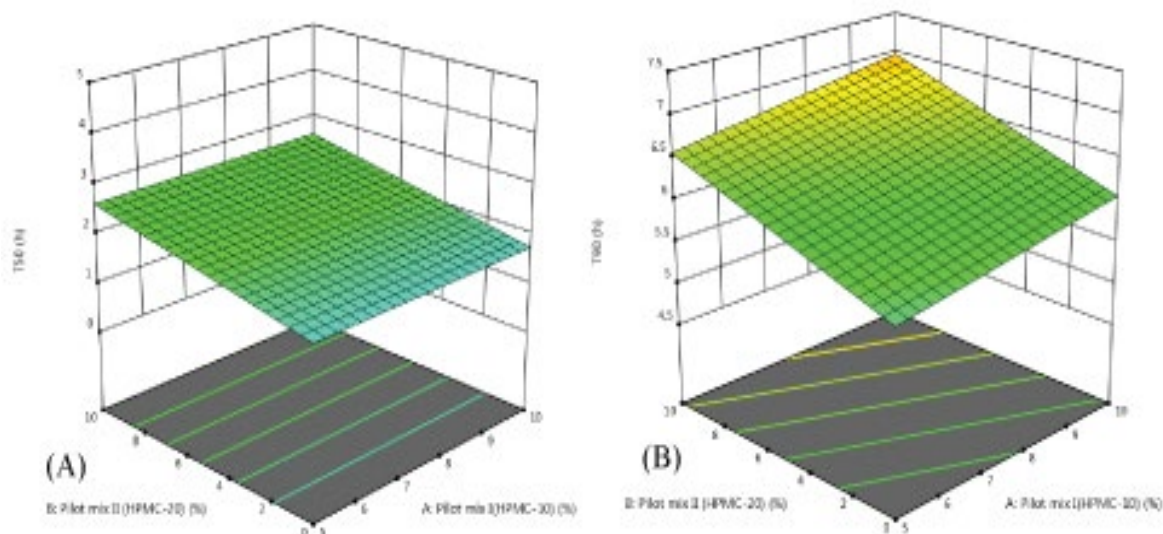


Fig. 4: Effect of percentage of pilot mix I and pilot mix II on (A):  $t_{50}$  and (B):  $t_{90}$  presented by response surface

TABLE 5: EVALUATION PARAMETERS OF THE OPTIMIZED FORMULATION

Parameters	Report
Average pellet size <sup>a</sup> (mm, n=20)	0.827
EE <sup>a</sup> (%)	94.06
TPCW <sup>a</sup> (% , n=5)	14.66
Angle of repose <sup>a</sup>	22.31±0.03
Bulk density <sup>a</sup> (g/cm <sup>3</sup> )	0.561
Tapped density <sup>a</sup> (g/cm <sup>3</sup> )	0.583
Carr's index <sup>a</sup> (%)	3.99
Hausner's ratio <sup>a</sup>	1.042±0.03
Friability <sup>a</sup>	0.09%
Content uniformity <sup>b</sup> (% , n=5)	119.67±2.66
Disintegration time <sup>b</sup> (min)	10.02
Weight variation <sup>b</sup> (% , n=20)	0.61
Zero-order <sup>b</sup>	0.9714
Sum of square	33.59
AIC	32.11

Note: <sup>a</sup>Properties of the pellets and <sup>b</sup>properties of the optimized batch

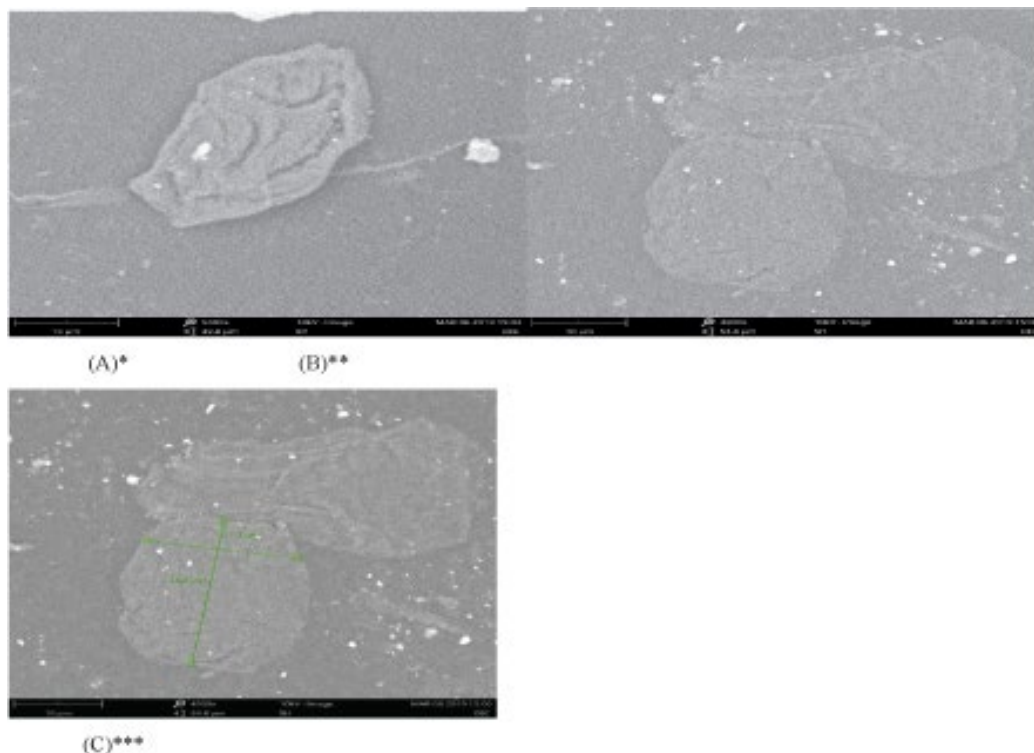
Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, Higuchi and Korsemeyar-Peppas) in order to describe the kinetics of drug release as shown in Table 5. Regression coefficient and slope (rate) were compared in all the formulations to study their effect on drug release. In addition, the optimized formula is also equipped with selective zero-order and Peppas models to calculate the residual sum of squares, Akaike Information Criteria (AIC) and the value of the best fit test ( $R^2$ ).

The surface of optimized formulation F9 pellets (HPMC-10 %) is continuous (fig. 5A), but compared

with smooth and uniform particles (fig. 5B, fig. 5C), it was coated with 20 % and 30 % HPMC for pilot mixing. The surface of the pill is dense, continuous and uniform. Therefore, at a higher coating level in the pilot mixture, the diffusion length of the dissolution medium in the drug layer and the diffusion of the dissolved drug will increase, which will result in a decrease in the release rate of formulation F9. These optimized timed-release pellets can release drugs *in vitro* for up to 7 h, which may be better than conventional dosage form, thereby reducing the frequency of dosing and improving patient compliance.

A 2<sup>3</sup> full-factorial design used for pre-mixing (pilot-mix) operations to obtain the desired release ( $t_{90}$ ) up to 7 h, as it was found to be one of the CPPs for timed-release pellets. The core, NPS prepared by using a sugar solution. A fluidized bed processor was used to coat diltiazem to the NPS. HPMC E15 used as a coating for NPS, with different percentages (10 % A, 20 % B, and 30 % C), divided into two levels (16.66 % and 33.33 %). According to the design matrix, pilot mixing was carried out for the *in vitro* dissolution studies and optimized batch was prepared for master blend and mixture based on the results. The Pareto charts supported the ANOVA results for the model simplification and eliminating non-significant terms ( $p > 0.05$ ). The optimal process variable (independent variable) selected to optimize the formulation of diltiazem timed-release pellets was set as the pilot mix I=24.9 %, pilot mix II=16.6 % and pilot mix III=16.6 %. Therefore, the pilot blend composed of 58.1 % of A, B and C coated pellets, and the remaining 41.9 % is uncoated NPS. The optimized pilot blend





**Fig. 5: SEM micrograph showing the size of pellets coated with (A): HPMC 10 %; (B): HPMC 20 % and (C) HPMC 30 %**  
**Note: \*Diameter range 0-10  $\mu$  and magnification 5400 x; \*\*Diameter range 0-10  $\mu$  and magnification 49 000 x and \*\*\*Diameter range 0-10  $\mu$  and magnification 4900 x**

showed desired release pattern of  $t_{50}$  was  $2.361 \pm 0.243$  h,  $t_{90}$  is 6.875 h.

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### Conflict of interests:

The authors declared no conflict of interest.

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