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A Review

Review on polymer selection and optimization of matrix tablets using systematic formulation strategies

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Despite the widespread use of polymeric matrix tablets for controlled and sustained drug release, rational selection and optimization of polymers remain challenging due to the complex influence of multiple formulation variables and their interactions. Although numerous polymers have been investigated for matrix tablets development, systematic approaches that efficiently evaluate their individual and interactive effects are required to improve formulation robustness. In this context, the present review focuses on the application of factorial design based experimental approaches in the formulation and optimization of polymeric matrix tablets. Studies employing 2^2, 3^2, and higher-order factorial designs are critically examined to demonstrate how polymer type, polymer concentration, and excipient interactions influence drug-release kinetics and critical quality attributes. The review highlights how factorial design facilitates identification of significant formulation variables, reduces experimental trials, and supports data-driven optimization of matrix tablets, thereby serving as a valuable tool for rational and efficient sustained-release formulation development.

Keywords: 2^2 factorial design, 3^2 factorial design, Critical Quality attributes, Experimental optimization, Hydrophilic polymers, Hydrophobic polymers

Introduction

The oral route is the most commonly employed delivery route of drug administration, since it is easy to administer, and relative to other routes, dosage forms are more freely designed using gastro intestinal physiology. Tablets are one of the common and traditional forms of oral solid dosage forms. Among oral dosage forms, tablets remain the most widely used because of their simplicity, stability, and ease of manufacture. Tablets are of various types such as coated, uncoated, buccal, sublingual, chewable, effusive, dispersible and modified release tablets. The modified-release drug delivery systems are designed to increase therapeutic effect by delivering the drug over a prolonged period[1]. The modified delivery drug release that is most popular is a matrix tablets that disperses drugs by a control mechanism, or diffusion, of dissolution. The active component is evenly distributed throughout the rate-controlling material, which may be mineral, lipid, plastic, hydrophilic, etc. This is a polymeric substance that slows down the release rate. Consequently, it inhibits local or systemic negative reactions by keeping the therapeutic concentration of the drug constant in the blood, and preventing fluctuations, including low or toxic concentrations to levels[2].

A matrix is a well-combined amalgamation of active pharmaceutical ingredient and polymers. The presence of stomach pH causes the drug in the matrix system to deteriorate slowly. This is a matter of two processes: linear erosion and, associated with it, a decreasing surface area, and dissolution of coated particles. The effect of this is a limited blood concentration of active pharmaceutical substances that are controllable, above the minimum effective concentration(MEC), and below the lethal level[3].

The application of the various polymers to alter the release of medications is the most important tool in making the matrix tablets. Some of the advantages of the use of matrix devices include a better safety margin of a strong medicine, maximization of drug use, a reduction in the variability of steady-state medicine levels, and a reduction in the number of times a medication can be administered to a patient, leading to an increase in medication adherence.

This review aims to discuss the materials used in the formulation of polymeric matrix tablets, their classifications, and the mechanisms governing drug release. In particular, it focuses on the application of Design of Experiments (DoE), especially factorial

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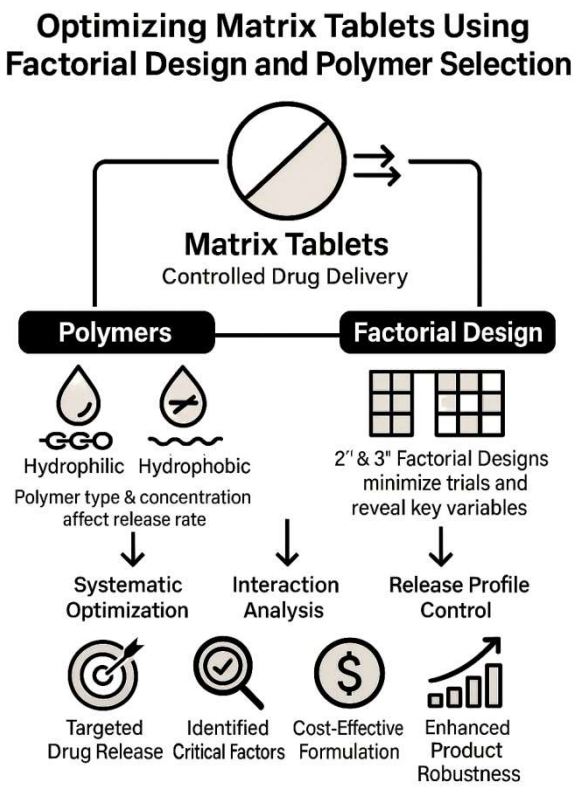

Graphical abstract

design approaches, for optimizing polymer selection and formulation variables in controlled-release matrix tablets. While earlier reviews largely emphasize polymer classification, release mechanisms, or general formulation strategies, the present review distinctly integrates polymer science with factorial design-based optimization. Studies employing 2^2, 3^2, and higher-order factorial designs are critically analyzed to elucidate the influence of formulation variables and polymer interactions on drug-release behaviour and tablet performance. By synthesizing optimization outcomes across diverse polymeric systems, this review highlights recurring formulation trends and demonstrates how factorial design enhances formulation robustness while reducing experimental burden, thereby providing a focused and practical reference for rational matrix tablets development.

Methodology

The literature reviewed in this article was collected through a systematic search of scientific databases including Scopus, PubMed, Science Direct, and Google Scholar. Keywords such as *matrix tablets*, *polymeric matrices*, *factorial design*, *design of experiments*, *controlled release*, and *sustained release formulations* were used either alone or in combination. The search primarily focused on articles published in peer-reviewed journals over the last two decades.

Matrix Tablets

Drug release is mainly controlled by diffusion, polymer swelling, erosion, or a combination of these mechanisms in matrix tablet systems, which are solid oral dosage forms in which the active pharmaceutical ingredient is evenly distributed within a polymeric network. The drug's physicochemical characteristics, the type and concentration of the polymer, and the matrix's structural features, such as porosity, all influence the predominant release mechanism. Because they rely on essentially different release principles, matrix systems should be distinguished from immediate-release, pellet-based, or multi particulate dosage forms for scientific clarity. Therefore, unless otherwise indicated, the classifications covered in this review are interpreted in the context of true matrix-based controlled or sustained-release systems.

Classification of Matrix Tablets

Matrix tablets can be broadly classified based on the nature of the matrix system and the predominant mechanism controlling drug release.

Lipid matrix system

Lipid wax matrices are composed of hydrophobic materials such as waxes, fatty acids, or glycerides that form a continuous matrix in which the drug is dispersed. Drug release is governed by the leaching of matrix layer, resulting in the formation of pores that permit water penetration and subsequent diffusion of the drug[4].

Mineral Matrices

Mineral matrices are primarily based on naturally derived polysaccharides such as alginates obtained from brown seaweed, which forms gel networks through ionic interactions. These polymers hydrate in aqueous media to form viscous gels that control drug release through swelling and diffusion mechanisms.

Hydrophilic Matrices

These systems swell upon contact with aqueous media, forming a hydrated gel layer that controls water penetration into the matrix. The outer gel layer gradually erodes over time, and the drug release is primarily governed by diffusion and it depends on the

type of hydrophilic polymer used, concentration and tablet geometry[5].

Inert polymer matrix systems

In this approach, drugs are encased by an inert polymer keeping them insoluble in the gastrointestinal fluids. Drug release occurs mainly by diffusion through capillary channels formed within the compressed polymer. The rate of release may be affected by alterations occur in the porosity, complexity of an inert matrix and, drug solubility[6].

Biodegradable Matrices

It is made of small pieces linked together. Bio-enzymes from nearby cells break down these materials into shorter chains[7].

Sustained Release Matrix Tablets

The delivery of drugs to the specific area in the body to achieve and maintain the desired drug concentration is the goal of any therapeutic delivery system. The two most significant ones are time-based delivery of drugs and spatial positioning, it directs a drug to a specific area and temporal delivery which controls the rate at which the drug reaches the required tissue. The delivery method of medication, physiological aspects, length of treatment and dosage of medication are all taken into consideration in enhancing sustained drug release. This has been facilitated by many factors such as the costliness of creating new drugs, exhaustion of transnational cases, identification of new polymeric accoutrements that can be employed to slow down the release of drugs, improvement of therapeutic safety and efficacy provided[8].

Matrix systems classification based on the type of polymer/s used

Hydrophilic matrices

Modified drug release is done using hydrophilic matrices. Direct compression of a blend comprising API and a share of the hydrophilic carriers, or wet granulation comprising of hydrophilic matrix and the drug substances, could be used to compress the matrix.

Many researchers have investigated the influences of formulation and processing variables on the mechanism of drug release of compressed hydrophilic matrices. The material has a rapid hydrating capability in the development of a matrix. Insufficient polymer hydration may lead to premature drug diffusion and compromised matrix integrity, resulting in uncontrolled release[9].

Hydrophilic matrix systems commonly employ the following polymer classes, selected based on drug solubility, desired release kinetics, and regulatory acceptance:

i. *Cellulose-based polymers:* Hydroxypropyl methylcellulose, Sodium Carboxy methyl cellulose
ii. *Non-cellulose natural polymers:* Lignin, Hyaluronic acid, Chitin, Alginate, Gelatin
iii. *Acrylic acid derivatives:* Polymethyl methacrylate, Carbopol 934, Polyacrylic acid

Hydrophobic Matrices

Hydrophobic matrix systems involves incorporating of drug within inert or water-insoluble polymers to form a rigid system to form the matrix. The main release mechanism is drug diffusion that takes place through capillary channels created between the compressed polymer particles[10]. Due to medicine must diffuse over a capillary network among compacted polymer particles, release is usually delayed. Direct compression of a drug mixture with plastic material yields plastic matrix tablets when the plastic material can transform into proper particles suitable for drug blending. These tablets contain embedded active drug within a porous and coherent skeletal structure.

For granulation, the tablet compression and entrapment can be achieved by,

- A solution of the plastic compound or another binder in an organic solvent can be used to mix and knead the solid medication and plastic powder before they are granulated.
- Using an organic solvent, the medication can be dissolved in the plastic and then granulated when the solvent evaporates.
- Drug and plastic masses are granulated using latex or pseudo-latex as the granulating fluid. e.g., Cellulose acetate, Polyvinyl chloride, and Polystyrene.

Fat-wax matrices

These tablets use a special fat-wax system to release medicine slowly. The drug is incorporated into lipid or wax based excipients such as beeswax. The drug release occurs slowly through diffusion across the waterproof wax layer, this provides prolonged therapeutic action and reduced dosing frequency[11].

Biodegradable matrices

Biodegradable matrix systems involve polymers that are degraded in a controlled manner within the body, in either an enzymatic or hydrolytic manner.

Both polymer degradation and diffusion regulate drug release and thus, they are ideal in targeted and responsive drug delivery[12].

Mineral matrix system

The hydrophilic carbohydrate polymeric material employed in this kind of matrix system can be extracted from brown seaweed species by using a diluted alkali solution.

Matrix system classification based on porous size

Micro-porous matrices

Microporous matrices contain pores with diameters typically ranging from 50 to 200A°, enabling diffusion-controlled drug release for low molecular size compounds[13].

Macro-porous matrices

In a macro-porous matrix system, the drug releases through pores with diameters between 0.1 to 1 μm. Drug molecules whose sizes are below 1 μm can be administered using this technology.

Non-porous matrices

Drug diffusion in this kind of matrix system happens *via* the network meshes as opposed to tiny pores.

Matrix system classifications based on alternative methods of preparation

Multilayered matrix system

In this matrix type of system, the drug molecules are encapsulated with a semipermeable material while the matrix core is made of hydrophilic material. The barrier layers can affect the core's swelling rate, which may reduce the exposure of the drug molecule to the environment for drug release. Different drug release rates occur due to the geometry of the barrier layer changing within the matrix. The rate of drug release is determined by the barrier layers of the matrix as they absorb water and swell, then gelate and dissolve[14].

Floating matrices

In a floating matrix system, the relative density is lower than the density of the gastric contents. Once buoyancy is achieved in the stomach, the API is released gradually from the matrix system. Drugs from this hydrophilic matrix technology are released continuously as long as the floating effect is controlled. HPMC is one of the common polymers in this type of drug-delivery system[15].

pH-sensitive matrix system

pH-sensitive matrix systems utilize polymers that remain intact in acidic environments and dissolve or swell at higher gastrointestinal pH values, enabling site-specific drug release. pH-sensitive polymers such as cellulose acetate phthalate or HPMC-phthalate are used. This matrix technology will disperse the enteric-coated drug in the GIT at a specific pH value that is high enough for drug absorption to occur[16].

Mucoadhesive matrices

Mucoadhesive matrix systems offer the ability to target multiple mucosal surfaces throughout the body for the localized or systemic delivery of drugs over extended periods. The polymers employed in this type of matrix system are swellable hydrophilic polymers. Mucoadhesion prolongs residence time at the absorption site, thereby enhancing drug bioavailability and therapeutic efficacy.

Systematic Formulation Strategies

Factorial design is an effective and strong experimental design applied to the study of the two or more independent variables (factors) together.

Factorial design has a number of types, including:

- Full Factorial Design: In this kind of design, all potential combinations of being studied variables are evaluated.
- Fractional Factorial Design: This kind of design implies the analysis of a sample of the possible combinations of the variables under investigation.
- Plackett-Burman Design: In this kind of design, a subset of all the potential combinations of the variables under investigation is evaluated, with the help of a particular design matrix.

Benefits of the factorial design

- Integrates quality into the product and the process, which is based on scientific knowledge.
- The specifications will depend on the performance of the product.
- Concentrate on control, comprehension and strength.
- The procedure is flexible to the design space.
- The report will be submitted based on the product and process knowledge[17].

Previous studies using factorial design for preparation of matrix tablets

Literature review of research that uses the factorial design-based optimization to design the matrix tablets formulations mentioned in the (Table 1). These research works demonstrate that factorial design has the potential to systematically compare formulation

Table 1 — Previous studies on matrix tablets using factorial design

Drug	Independent variable	Dependent variable	Reference
Cephalexin	HPMC K15M (X_1) HPMC 15cps (X_2)	Drug release(DR) in 1 hr(Y_1), DR in 2 h (Y_2), DR in 4 h (Y_3)	(18)
Captopril	HPMC K4M (X_1) Concentration of EC in Ethanol (X_2)	Hardness (Y_1), % friability(Fb) (Y_2), *In vitro* drug dissolution profile (Y_3)	(19)
Diacerein	Type of carrier (X_1), Drug: carrier ratio (X_2), Evaporation technique (X_3)	Solubility (Y)	(20)
Capecitabine	HPC (X_1), Sodium alginate (X_2)	*In vitro* DR (Y_1), swelling index(SI) (Y_2)	(21)
Terbutaline sulphate	Type of lipid (X_1), lipid-drug ratio (X_2), type of filler (X_3)	% DR in 8 h (Y_1), % DR in 12 h (Y_2), % DR in 24 h (Y_3)	(22)
Celecoxib	Total solid content %(X_1), drug:P1:P2 ratio (X_2)	Particle size (Y_1), Polydispersity index(PDI) (Y_2), Assay (Y_3)	(23)
Valacyclovir Hcl	Polyox WSR303 (X_1), Sodium starch glycolate (X_2)	% DR in 12 h (Y_1), FLT (Y_2), maximum % of swelling (Y_3)	(24)
Losartan Potassium	PEG 6000 (X_1), PVP K30 (X_2)	Pellet wet mass (Y_1), ratio of binder for pellet wet massing (Y_2), particle size of pellet (Y_3), % DR in 8 h (Y_4)	(25)
Levofloxacin	Eudragit RS (X_1), Carbopol (X_2)	% DR in 6 h (Y_1),% DR in 12 h (Y_2), % DR in 24 h (Y_3), Mucoadhesion time (Y_4), mucoadhesive strength (Y_5), SI (Y_6)	(26)
Atenolol	Polymer ratio (X_1), Guar gum to Xanthan gum ratio (X_2)	Floating time (Y_1), Diffusion exponent(DE) (Y_2) ,$t_{50\%}$ (Y_3)	(27)
Amisulpride- Labrasol	Type of polymer (X_1), Polymer concentration (X_2)	% DR in 2 h (Y_1), % DR in 8 h (Y_2)	(28)
Bisoprolol fumarate	Calcium alginate (X_1), HPMC K4M (X_2), Carbopol 943 (X_3)	% DR in 6h(Y_1), hardness (Y_2)	(29)
Verapamil HCl	HPMC K15 CR (X_1), Eudragit RSPO (X_2)	% DR in 18h (Y_1), % DR in 20 h (Y_2)	(30)
Diclofenac sodium	Karaya gum (X_1), Ghatti gum (X_2)	% DR in 1h (Y_1), % SR in 12h (Y_2), DE (Y_3), $t_{50\%}$ (Y_4)	(31)
Tolperison HCL	Cetyl alcohol (X_1), HPMC K100M (X_2)	% SI (Y_1), $t_{50\%}$ (Y_2), $t_{90\%}$ (Y_3)	(32)
Promethazine HCL	Eudragit E100 (X_1), Crospolividone (X_2), Na. stearyl fumarate (SSF) (X_3)	Hardness of tablets(Y_1), tablet DT (Y_2), tablet initial rate of dissolution (IDR) (Y_3), Tablet Dissolution Efficiency (TDE) (Y_4)	(33)
Losartan Potassium	HPMC K4M (X_1), $NaHCO_3$ (X_2), Ethyl cellulose (X_3)	% CDR (Y_1), FLT (Y_2), % Swelling index (Y_3), $t_{50\%}$ (Y_4)	(34)

and process variables which influence crucial properties such as drug release (DR), floating lag time (FLT), time to 50% and 90% drug release (t50 and t90) as well as hardness, friability (Fb), swelling index (SI) and dissolution time (DT).

In more than a few studies, the influence of polymer type and concentration on drug release was investigated on the basis of 2^2 and 3^2 factorial designs. Formulations of Mitiglinide, Cephalexin, Atenolol, and Captopril prove that it is possible to select all the HPMC grades, independently or in combination with other polymers to obtain the desired control of sustained drug delivery in 6-12 h. The literatures also provide the effects of interactions between the variables of formulation in determining the integrity of a matrix and diffusion-controlled release systems.

Other research works on Diclofenac sodium, Aceclofenac and Bisoprolol research demonstrates that factorial design is ideal to uncouple the interplay between polymer concentration and compression force on tablet hardness, friability and drugs release kinetics. These results highlight the usefulness of factorial design to find a trade-off between mechanical strength and controlled drug release.

The power of factorial design to discover synergistic interactions between polymers that control gastric retention and extended release is demonstrated in the work of a number of investigators in mixed polymer using systems like Eudragit with HPMC or Gelucire. On the same note, optimization of floating matrices with Repaglinide and Atenolol have shown that gas-generating agents such as sodium bicarbonate ($NaHCO_3$) are the ones that optimize buoyancy and dissolution.

The analyzed review support the information about factorial design which is an efficient and statistically sound tool of discovering the mechanistic details of polymer and drug interaction. It decreases the number of experimental efforts, and produces predictable and reproducible performance in polymeric matrix tablets formulations.

Polymer selection

Polymeric matrix systems offer effective control over drug release, optimizing polymer type and formulation variables remains a major formulation challenge. Factorial design requires coming up with a design matrix containing all the combinations of variables under consideration. Experiments and data collection are then carried out by the use of the design matrix. Statistical methods like ANOVA (analysis of variance) are then used to analyse the data so as to arrive at the significance of the variables and the relationship between them.

To generate the matrix tablets, various kinds of polymers are applied depending on the physico-chemical nature of the drug substance to be incorporated into the matrix system. The type of polymers utilized in the process of making matrix tablets are provided below[35].

The hydrogels include polyvinyl alcohol (PVA), polyacrylic acid (PAA), and polyacrylamide (PA). Among soluble polymers, there are methylcellulose (MC), polythene glycol (PEG), and polyacrylic acid (PAA). Biodegradable polymers include polyhydroxy-alkanoates (PHA), polybutylene succinate (PBS) and polythene succinate (PES). Non-biodegradable polymers are poly-styrene (PS), polyethene (PE) and ethyl cellulosic (EC). Cashew gum, ghatti gum, chitosan and locust bean gum are all natural gums. Some of the mucoadhesive polymers are polyacrylic acid (PAA), polycarbophil, pectin and hyaluronic acid (HA).

Preparation methods

Various manufacturing techniques such as Direct Compression, Wet Granulation and Dry granulation are used to prepare matrix tablets, depending on the physicochemical properties of the drug and polymers used are mentioned below.

Direct compression

Direct compression is the simple compression of API and polymers without changing the drug's physico-chemical properties. Pre-milling of the ingredients is part of the direct compression process-specifically the particle size reduction of the API and excipients. Pre-milling facilitates achieving a uniform particle size distribution. The pre-milled ingredients, along with the excipients, are then blended to improve powder flow properties. The blended powder is then compressed into tablets using a tablet punching machine[36]. The process of preparation of matrix tablets by the direct compression method is given in (Fig. 1).

Wet granulation

The wet granulation method involves blending polymer and API with a sufficient quantity of binders. Once the mixture was sufficiently cohesive, it was run through sieve number ten and dried in a drying oven at 40°C for 30 min. Granules that are dry will be run through sieves 22 and 44. The granules that pass through sieve number 44 will be gathered and mixed with 15% fine particles. After adding lubricants and glidants, the tablets are compressed using a tablet compression machine[37]. The process of preparation of matrix tablets by the wet granulation method is given in (Fig. 2).

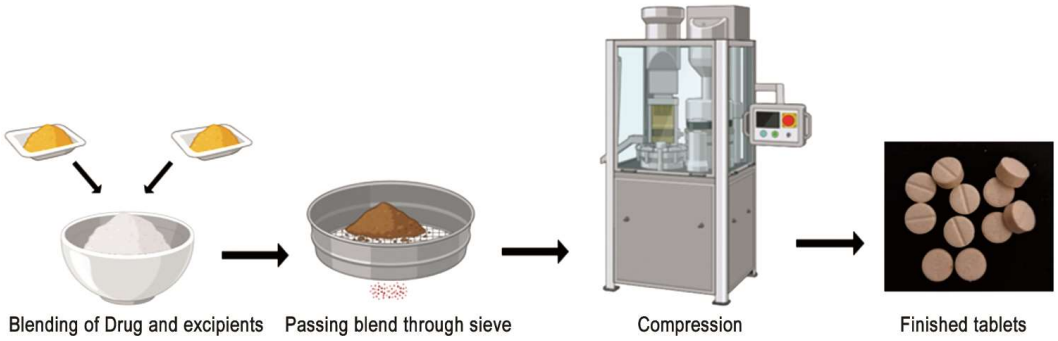

Fig. 1 — Schematic representation of matrix tablet preparation by direct compression, illustrating blending of the active pharmaceutical ingredient with matrix-forming polymers followed by tablet compression. This method highlights the role of polymer type, particle size, and compression force in controlling matrix integrity and drug-release behavior

Dry granulation

The cube mixer was used to blend API drug and polymer during a period of fifteen min. The mixture obtained was pressed in round tablets of diameter 20 mm. The pills were crushed using a double-roll crusher. The granular material was then finally filtered with a 40-mesh sieve in order to select the appropriate size fraction. The granules are pressed into a tablet by using a tablet punching machine. The process of preparation of matrix tablets by the dry granulation method is given in (Fig. 3).

High shear granulation

The weighted amount of API and polymers was put into the high-speed granulator bowl and swirled 60 sec. This was performed with a minimum speed of

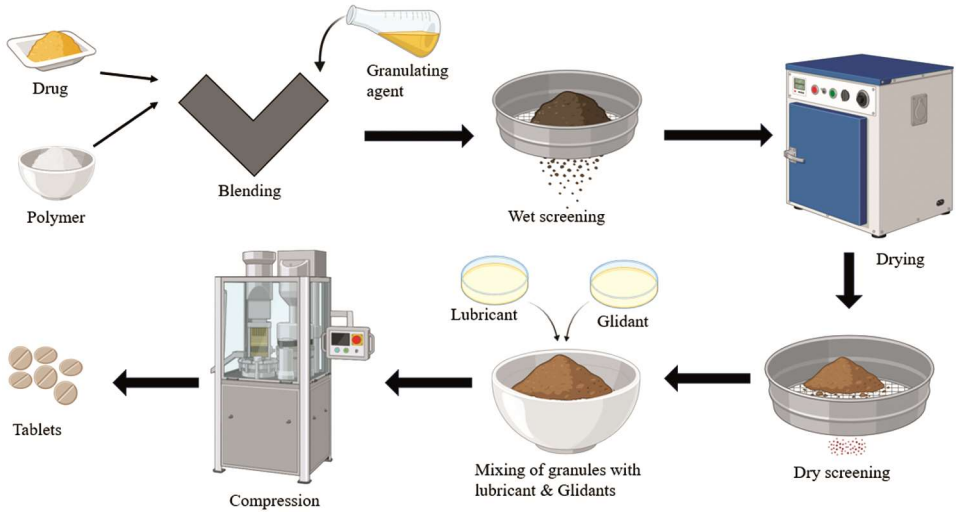

Fig. 2 — Schematic illustration of matrix tablet preparation by wet granulation, showing binder addition, granule formation, drying, and compression. Wet granulation improves content uniformity and matrix cohesion, thereby influencing diffusion- and erosion-controlled drug release

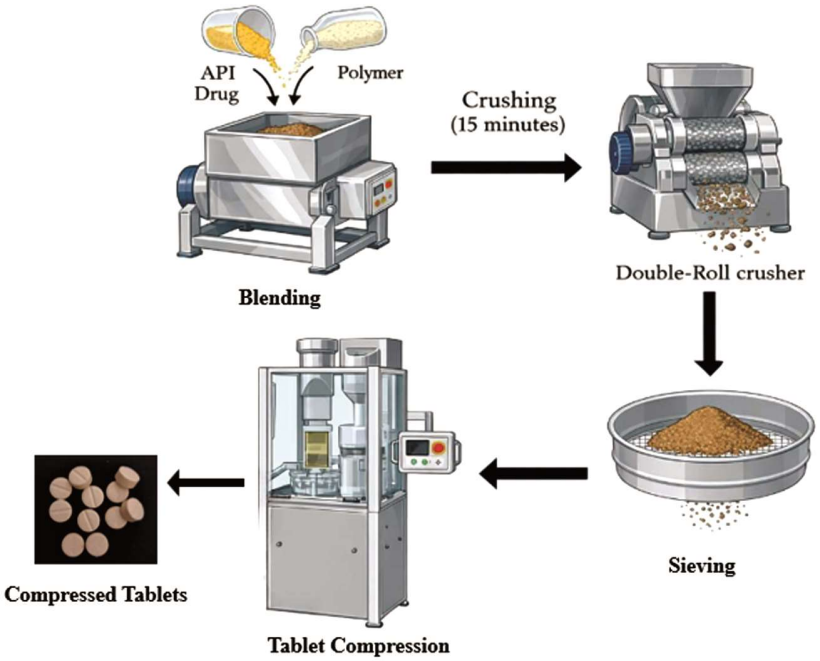

Fig. 3 — Schematic representation of dry granulation (slugging or roller compaction) for matrix tablet preparation. This process enables granule formation without liquid binders and is particularly suitable for moisture- or heat-sensitive drugs while maintaining controlled-release performance

the blender and cutter in which contents were gradually collected by adding distilled water and massed in three min on rapid rotation of the blades. The obtained particulate matter was stored in the fluid-bed drier to dry and then filtered over the 25-mesh sieve using an oscillating granulator. The granules are pressed into a tablet with the help of a tablet punching machine[38]. The process of preparation of matrix tablets by the high shear granulation method is given in (Fig. 4).

Hot melt granulation

V-shell blender was used in the mixing of the API and excipients at 25 rpm over 20 min and the mixture was sieved through sieve number 35 to remove any lumps. The fully intermeshing extruder, which was equipped with a new screw set was then operated to process the hot-melted granulations without extrusion die. The eight-part extruder barrel area was divided and the physical mixture is injected in the first zone called the feeding zone and not heated. Zones 2, 3 were maintained at 110°C, zone 4 was at 70°C, and the rest of the zones were maintained at 50°C according to preliminary research. The preset temperatures in all the zones were kept at temperatures lower than the melting point of the API.

The adjusted rotating screw design involves mixing components in two locations, one of them being in zone 3 and the second, immediately preceding the discharge components. The extruder was then left to stabilize at a given temperature of 30 min and then the trials commenced. The physical mixes were then subjected to a volumetric feeding process whereby the combination was fed through feeding section to the extruder and processed through the barrel at the required temperatures.

The screw speed was set at 100 rpm and powder feed rate was set at 7.2 g/min, maintained constant. When the steady-state conditions were achieved, granules could be collected using the open end of the extruder. After granulation, the collected grains were taken in closed pouches which were covered with foil. The granules are compressed into tablets by a tablet punching machine[37]. The process of preparation of matrix tablets by the hot melt granulation method is given in (Fig. 5).

Evaluation parameters

Preformulation studies

Angle of repose

The angle of repose is known to be measured either through the fixed funnel or the free-standing cone method. The funnel is placed on a flat surface with its tip raised at a particular height (H) above a piece of graph paper. Powder or granules are then poured into the funnel slowly until the tip is defining the top of the pile below. The radius (r) of the base of the heap is measured in order to determine the angle of repose.

$$\text{Tan}\phi = \frac{\text{height of pile}}{\text{radius of pile}}$$

Bulk density

The bulk density was calculated by weighing a sample of the API and polymer mixture and transferring it to a calibrated cylinder. The volume

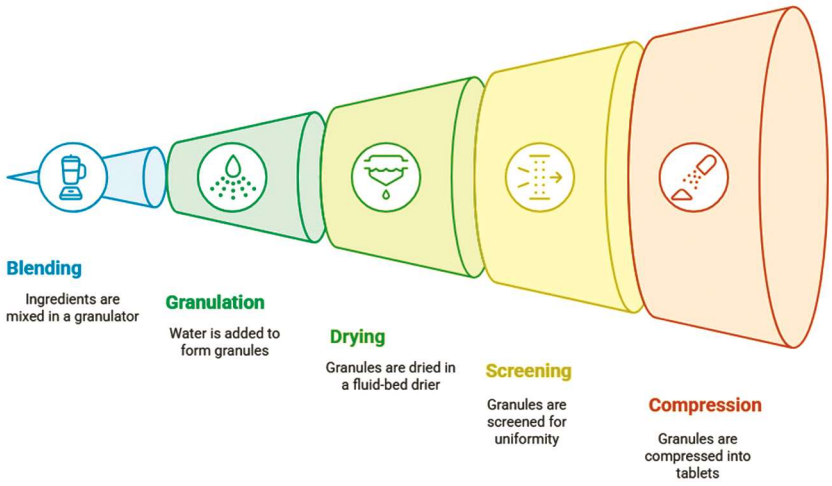

Fig. 4 — Schematic overview of high shear granulation for matrix tablet formulation, demonstrating rapid and uniform granule formation under high mechanical energy. This technique enhances polymer distribution within the matrix, contributing to reproducible drug-release characteristics

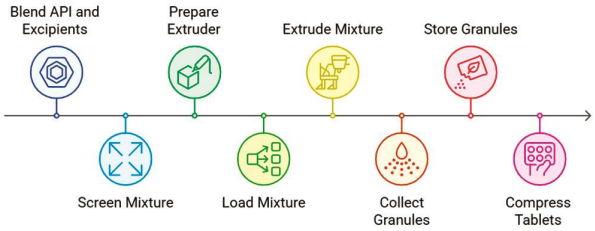

Fig. 5 — Schematic illustration of hot melt granulation for matrix tablet preparation, in which molten lipid or polymeric excipients act as binders. This solvent-free process enables uniform drug dispersion within the matrix and is particularly advantageous for sustained-release formulations

was recorded, and it can be determined by using the following formula,

Bulk density = weight of mixture/volume of mixture

Tapped density

In a measuring cylinder, a weighed volume of mixture was tapped for a predetermined amount of time, and the resulting reduced volume was recorded. The following formula was then used to get the tapped density[38].

Tapped density = weight of mixture/volume of mixture

Hausner's Ratio

It is the ratio of the tapped density of a powder to the bulk density of the powder. It could be used to give an index of the flow characteristic of powder. The force behind this is that, cohesive powders possess greater surface attractive force and, as a result, particles can resist gravity and suspend themselves between the void spaces. With further force exerted by tapping, particles are deposited into the voids and the volume of the powder is reduced and the bulk density increases. Then Hausner Ratio was obtained using the following formula[39].

Hausner Ratio = tapped density/bulk density

Carr's Compressibility Index

Carr's identified an indirect way of defining powder flowability, that is, measurements of bulk densities. Relative compressibility of a powder is a direct indicator of the strength and stability of powder blend which is represented as the susceptibility of the powder blend to arch. The Index value of the Carr's can be obtained through the following formula[40].

$$\text{Carr"s index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Total porosity

The percentage of a material's total volume that is made up of void spaces, or pores, is called total porosity. In the case of powders and granules, it describes the proportion of the bulk volume that is not taken up by solid particles. Using the following formula, total porosity can be determined from the initial volume and tapped volume of the same granules.

$$\text{Total porosity} = \frac{\text{initial volume} - \text{tapped volume}}{\text{initial volume}} \times 100$$

Post-formulation studies

***In vitro* dissolution studies**

In vitro dissolution study is performed by using paddle apparatus at 50 rpm. There were two phases to the dissolution experiments and to begin with, the dissolving medium for the initial two hours with acid buffer of pH 1.2, identical to the environment in the gastrointestinal tract and with the intestinal environment, phosphate buffer at pH 6.8, maintained at 37 ± 0.5°C was utilized as the dissolving medium for the subsequent 10 h., dissolution was performed[41].

Weight variation test

20 tablets is used by taken randomly and their weight is determined to find the average mass, which is then compared with the mass of an individual tablet. Percentage weight variation is calculated as per the specifications given in the Indian Pharmacopeia.

Hardness Test

The hardness of the tablets is determined with the aid of a tablet hardness tester. Zero the scale and place the tablet between the fixed and the movable jaws. The force was slowly increased until the tablet was broken. The breaking load was measured as a hardness value in kg/cm².

Content Uniformity

Ten tablets from preparation is randomly selected made in to fine powder. After isolating the API powder in 100 mL of phosphate buffer pH 6.8, the solution was filtered. Absorbance is measured by using a UV-Visible spectrophotometer at an appropriate wavelength in order to determine the content after proper dilution with phosphate buffer pH 6.8. The drug content is ascertained using a calibration curve[42].

Friability

Friability is measured in a friability test apparatus by placing 10 tablets and rotating them at 25 rpm for 4 min. The tablets are dedusted using a soft muslin

cloth and reweighed after which the weight loss is calculated as a percentage of initial weight[43].

Thickness and diameter

The thickness and diameter of the tablet is determined using a Vernier calliper. Ten tablets from each formula is randomly selected for this measurement, and the thickness and diameter of each tablet is measured.

Drug contents

Five tablets is powdered and equivalent weight of drug is dissolved by stirring constantly and make up to 100 ml and then the solution was filtered. Upon filtration, solution is again diluted using distilled water and absorbance was measured at the appropriate wavelength[44].

Swelling and erosion behaviour

The swelling and erosion behaviour of the matrix tablets is tested by determining the swelling index. Three tablets are taken and weighed individually, the tablets are immersed in distilled water. The tablets are removed from the water after each one hour, and excess water is drained out with filter paper. Once again, the tablets are weighted. The swelling index can be calculated using the below formula[45].

$$\text{Swelling index} = \frac{\text{weight at time (t)} - \text{initial weight}}{\text{initial weight}} \times 100$$

Future prospects

Matrix tablets hold great future potential because they have several advantages when it comes to drug delivery, especially controlled and sustained-release drug formulations.

Some of the major future potential areas are as follows:

1. **Controlled drug delivery systems**
- Matrix tablets will remain important in delivering drugs at a controlled rate, which will improve patient compliance.
- They can minimize dosing frequency and ensure constant drug plasma levels.
- With 3D printing and computer-aided drug design, matrix tablets can be engineered for individualized drug regimens.
- Customized matrix systems can allow for targeted drug release

2. **Combination therapy**
- Matrix tablets can allow simultaneous delivery of two or more drugs in a single drug product, which is particularly useful for chronic conditions such as diabetes, hypertension, and cancer.
- Multi layered matrix systems will facilitate improved management of comorbidities.

3. **Nanotechnology integration**
- Bioavailability and drug targeting can be improved through nanoparticle and nanocarrier particles incorporated in matrix tablets.
- It is especially beneficial for drugs that are poorly soluble and poorly permeable.

4. **Utilization of biodegradable and natural polymers**
- Biopolymers such as chitosan, alginate, and cellulose derivatives are being increasingly considered for the development of environmentally friendly matrix tablets.
- They provide improved biocompatibility and controlled degradation.

5. **Gastroretentive and site-specific delivery**
- Gastric-retentive float or expandable matrix tablets have the potential to improve the bioavailability of drugs with limited absorption windows. Targeted delivery to specific regions of the gastrointestinal tract is also a key area of development.

6. **Incorporation of smart polymers**
- Stimuli-sensitive polymers (temperature-sensitive, for example) can design smart matrix tablets that release medication following environmental stimuli.

7. **Regulatory and commercial development**
- With greater need for patient-focused drug delivery systems, matrix tablets will face greater regulatory approvals.
- Pharmaceutical companies will keep investing in research and development of new matrix tablets designs.

8. **Drug abuse prevention**
- Matrix technology containing formulations may deter abuse by providing tamper-resistant drug delivery.

Conclusion

Matrix tablets continue to be a pillar of prolonged and controlled drug release, with polymer choice being an important means of controlling drug release. This article emphasizes the knowledge on polymeric matrix tablet formulation with specific focus on the application of factorial design based optimization strategies. Through systematic assessment of the impact of more than

one formulation variable, including polymer type, concentration, and excipient interactions, factorial design makes it a cost-effective and efficient method for obtaining desired drug release patterns. Across hydrophilic, hydrophobic, lipid-based, and mixed polymer systems, factorial design has consistently enabled systematic identification of significant formulation variables and interaction effects that are not readily captured through conventional trial-and-error approaches. Applications involving 2^2, 3^2, and more extensive factorial designs have proven to be efficacious in the evaluation of critical formulation factors, reducing experimental trials, and enhancing product robustness. Coupling polymer science with the design of experiments improves the accuracy and replicability of matrix tablets designs and, ultimately, pharmaceutical results. The evidence reviewed supports the integration of factorial design as a standard methodology in the development of controlled and sustained release matrix tablets formulations.

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Conflict of interest

All authors declare no conflict of interest.

References

1 Williams R, Cauldbeck H & Kearns V, Sustained-release drug delivery systems. *Eye*, (2024) 1.

2 Chen K, Li B, Xu H, Wu J, Li J, Sun W, Fang M, Wang W, Wang S & Zhai Z, Zeolitic imidazole framework-8 loaded gelatin methacryloyl microneedles: A transdural and controlled-release drug delivery system attenuates neuroinflammation after spinal cord injury. *Int J Biol Macromol*, 256 (2024) 83.

3 Hye T, Moinuddin SM, Sarkar T, Nguyen T, Saha D & Ahsan F, An evolving perspective on novel modified release drug delivery systems for inhalational therapy. *Expert Opin Drug Deliv*, 20 (2023) 335.

4 Nokhodchi A, Raja S, Patel P & Asare-Addo K, The role of oral controlled release matrix tablets in drug delivery systems. *BioImpacts*, 2 (2012) 175.

5 Nagendrakumar D, Keshavshetti GG & Shardor AG, An overview: Matrix tablets as sustained release. *Recent Res Sci Technol*, 5 (2013) 36.

6 Sriamornsak P, Thirawong N & Korkerd K, Swelling, erosion and release behavior of alginate-based matrix tablets. *Eur J Pharm Biopharm*, 66 (2007) 435.

7 Bisht T, Rishiwer P & Kumar P, Review on matrix tablet. *MATRIX*, 4 (2016) 6.

8 Reynolds TD, Mitchell SA & Balwinski KM, Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. *Drug Dev Ind Pharm*, 28 (2002) 457.

9 Quinten T, De Beer T, Vervaet C & Remon JP, Evaluation of injection moulding as a pharmaceutical technology to produce matrix tablets. *Eur J Pharm Biopharm*, 71 (2009) 145.

10 Nisha S, Mathew G & Lincy J, Matrix tablets: an effective way for oral controlled release drug delivery: Controlled drug delivery using matrix tablets. *Iran J Pharm Sci*, 8 (2012) 165.

11 Corti G, Cirri M, Maestrelli F, Mennini N & Mura P, Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin. *Eur J Pharm Biopharm*, 68 (2008) 303.

12 Rao VM, Engh K & Qiu Y, Design of pH-independent controlled release matrix tablets for acidic drugs. *Int J Pharm*, 252 (2003) 81.

13 Streubel A, Siepmann J & Bodmeier R, Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *Eur J Pharm Sci*, 18 (2003) 37.

14 Xu G & Sunada H, Influence of formulation change on drug release kinetics from hydroxy propyl methyl cellulose matrix tablets. *Chem Pharm Bull*, 43 (1995) 483.

15 Dash TR & Verma P, Matrix tablets: An approach towards oral extended release drug delivery. *Int J Pharma Res Review*, 2 (2013) 12.

16 Sriamornsak P, Thirawong N, Weerapol Y, Nunthanid J & Sungthongjeen S, Swelling and erosion of pectin matrix tablets and their impact on drug release behavior. *Eur J Pharm Biopharm*, 67 (2007) 211.

17 Bibby DC, Davies NM & Tucker IG, Mechanisms by which cyclodextrins modify drug release from polymeric drug delivery systems. *Int J Pharm*, 197 (2000) 1.

18 Jishnu V, Gilhotra R & Prabhakaran R, Formulation and evaluation of cephalexin extended release matrix tablets using 3^2 factorial design. *J Young Pharm*, 3 (2011) 259.

19 Pandya VP, Patel VB & Patel P, Formulation, evaluation and optimization of sustained release matrix tablets of captopril. *J Pharm Bioallied Sci*, 4 (2012) S77.

20 Soliman MAN, Ibrahim HK & Nour SAE-K, Diacerein solid dispersion loaded tablets for minimization of drug adverse effects: statistical design, formulation, *in vitro* and *in vivo* evaluation. *Pharm Dev Technol*, 26 (2021) 302.

21 Gaikwad SS, Avhad RD & Kalkotwar RS, Formulation, development and *in vitro* characterization of modified release tablets of capecitabine. *Drug Dev Ind Pharm*, 46 (2020) 20.

22 Hashem FM, Nasr M, Fathy G & Ismail A, Formulation and *in vitro* and *in vivo* evaluation of lipid-based terbutaline sulphate bi-layer tablets for once-daily administration. *AAPS PharmSciTech*, 17 (2016) 727.

23 Figueiredo J, Mendes M, Pais A, Sousa J & Vitorino C, Microfluidics-on-a-chip for designing celecoxib-based amorphous solid dispersions: when the process shapes the product. *Drug Deliv Transl Res*, 15 (2025) 732.

24 Upadhyay P, Nayak K, Patel K, Patel J, Shah S & Deshpande J, Formulation development, optimization and evaluation of sustained release tablet of valacyclovir hydrochloride by combined approach of floating and swelling for better gastric retention. *Drug Deliv Transl Res*, 4 (2014) 452.

25 Abou Obaid NI, Al-Jenoobi FI, Ibrahim MA & Alam MA, Losartan potassium sustained release pellets with improved in vitro and in vivo performance. *Pharm Dev Technol*, 25 (2020) 1031.

26 Abd El-Bary A, Kamal Ibrahim H, Haza'a BS & Al Sharabi I, Formulation of sustained release bioadhesive minitablets containing solid dispersion of levofloxacin for once daily ocular use. *Pharm Dev Technol*, 24 (2019) 824.

27 Dey S, Mazumder B, Chattopadhyay S, Das MK, Sinha S, Ganguly S, De K & Mishra M, Polymers derived from *Xanthomonas campesteris* and *Cyamopsis tetragonolobus* used as retardant materials for the formulation of sustained release floating matrix tablet of atenolol. *Int J Biol Macromol*, 65 (2014) 346.

28 Younes NF, El Assasy AE-HI & Makhlouf AI, Micro-environmental pH-modified Amisulpride-Labrasol matrix tablets: development, optimization and in vivo pharmacokinetic study. *Drug Deliv Transl Res*, 11 (2021) 103.

29 Malakar J, Nayak AK & Goswami S, Use of response surface methodology in the formulation and optimization of bisoprolol fumarate matrix tablets for sustained drug release. *Int Sch Res Notices*, 12 (2012) 624.

30 Baviskar D, Sharma R & Jain D, Modulation of drug release by utilizing pH-independent matrix system comprising water soluble drug verapamil hydrochloride. *Pak J Pharm Sci*, 26 (2013) 137.

31 Reddy S, Shivakumar H, Shyam MM, Narendra C & Moin A, Karaya and ghatti gum as a novel polymer blend in preparation of extended release tablets: optimization by factorial design. *J Drug Deliv Sci Technol*, 24 (2014) 525.

32 Patel AU, Caudhari DV, Shah PJ & Shah SA, Hot melt granulation method for the preparation of floating matrix tablets of Tolperisone Hydrochloride. *Future J Pharm Sci*, 4 (2018) 139.

33 Alyami HS, Ibrahim MA, Alyami MH, Dahmash EZ, Almeanazel OT, Algahtani TS, Alanazi F & Alshora DH, Formulation of sublingual promethazine hydrochloride tablets for rapid relief of motion sickness. *Saudi Pharm J*, 29 (2021) 478.

34 Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, Foudah AI, Alrobaian MM, Shukla R, Singh S & Kesharwani P, Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. *Heliyon*, 6 (2020) 11.

35 Panigrahi KC, Patra CN, Jena GK, Ghose D, Jena J, Panda SK & Sahu M, Gelucire: A versatile polymer for modified release drug delivery system. *Future J Pharm Sci*, 4 (2018) 102.

36 Tadros MI, Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers. *Eur J Pharm Biopharm*, 74 (2010) 332.

37 Teixeira MT, Sa-Barreto LL, Taveira SF, Gratieri T, Gelfuso GM, Marreto RN, Silva IC & Cunha-Filho M, The influence of matrix technology on the subdivision of sustained release matrix tablets. *AAPS PharmSciTech*, 21 (2020) 9.

38 Nautyal U & Gupta D, Oral sustained release tablets: an overview with a special emphasis on matrix tablet. *Int J Health Biol Sci*, 3 (2020) 6.

39 Petrović J, Ibrić S, Betz G & Đurić Z, Optimization of matrix tablets controlled drug release using Elman dynamic neural networks and decision trees. *Int J Pharm*, 428 (2012) 57.

40 Tolia G & Li SK, Study of drug release and tablet characteristics of silicone adhesive matrix tablets. *Eur J Pharm Biopharm*, 82 (2012) 518.

41 Prakhar A & Semimul A, A comprehensive review on sustained release matrix tablets: a promising dosage form. *Univ J Pharm Res*, 3 (2018) 222.

42 Songire PR, Aher SS & Saudagar R, Recent research on matrix tablets for controlled release-a review. *Asian J Pharm Technol*, 5 (2015) 214.

43 Veronica N, Heng PWS & Liew CV, Alginate-based matrix tablets for drug delivery. *Expert Opin Drug Deliv*, 20 (2023) 115.

44 Zalte H & Saudagar R, Review on sustained release matrix tablet. *Int J Pharm Biol Sci*, 3 (2013) 17.

45 Furlanetto S, Cirri M, Maestrelli F, Corti G & Mura P, Study of formulation variables influencing the drug release rate from matrix tablets by experimental design. *Eur J Pharm Biopharm*, 62 (2006) 77.