How to Cite:
Sharma, P. K., Shukla, V. K., Kumar, A., & Sharma, R. (2022). Developing new treatment modalities from poorly dissolvable antihypertensive: Courtesy delivery system design &niche technologies. *International Journal of Health Sciences*, *6*(S3), 12535–12560. https://doi.org/10.53730/ijhs.v6nS3.6898

Developing new treatment modalities from poorly dissolvable antihypertensive: Courtesy delivery system design &niche technologies

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Abstract---Most antihypertensive drugs have impaired dissolution rate and result from poorly aqueous solubility, polymorphic modifications, structure-based H-bond donor or acceptor anamolies. These physical attributes would have detrimental effects and may cause an entity out of the race from efficacious candidates. Nevertheless, compliance with the dissolution rate must be fulfilled under the regulatory mandate and serve as an assessment tool for product performance. The present reviews the niche technologies like electrospinning, spraying, or mesoporous methods that led to the generation of more dissolvable antihypertensives. Several drug delivery systems design allows the incorporation of surfactants, microenvironment dissolution rate modifiers, acidifiers that could improve the dissolution rate of antihypertensives are reviewed.

Keywords---poor solubility, ternary dispersion, amorphization, nano-suspension, nano-particles, antihypertensive, SEDDS, SNEDDS, spin.

Introduction

Hypertension is a sedentary lifestyle condition manifested by elevated pressure in the blood carry vessels exceeding normal levels. Primary factors associated with its occurrence are stress, heart diseases, obesity, consumption of alcohol, lack of exercise, smoking, growing age, etc. (Yin X et al., 2019). Moreover, it affects the normal functioning of body organs, responsible for severe health complications, including, e.g., strokes, heart attack, organ system failure, etc. Therefore, various therapeutic agents under different drug categories in the treatment of hypertension are usually administered for long-term therapy (Yasser M et al., 2019).

Current therapy is always searched for risk-benefit factors and therefore requires newer antihypertensive agents with minimal side effects and high comparative efficacy over the existing ones. Usually, this demand for newer therapeutic agents is expected to meet through the drug development process, which is complicated, tedious, exhaustive, revenue spending, and requires considerable time and work. Furthermore, the regulatory approval process for new entrants is continuously evolving to appraise new drug safety and efficacy standards (Srivastava D et al., 2019). In these hindrances, the focus has been shifted from new drug development to work on already approved drugs either through new strategies of formulation design or technologies-driven products. In addition, techniques have been adopted to explore existing drugs through improving efficacy and finding new indications (Mishra J et al., 2019).

Major concerns of the various delinquent areas in the already approved drugs are their less efficacy and lesser bioavailability due to their impaired physicochemical properties like dissolution and poor aqueous solubility. These are concerned with the thrust area in the preformulation and formulation development (Meruva S et al., 2019). For example, the antihypertensive class and its subcategories exhibited poor dissolution behavior and drug candidates, as discussed in Table 1. Several dissolutions enhancing methodologies and formulation strategies have been investigated to improve the dissolution characteristics of poorly soluble drugs belonging to antihypertensive medicines are given in the table, during the early stage of NDA filing of such medicate two-stage process that dealt with poor dissolution behaviours. It was primarily attempted when a poorly soluble compound was preclinical before IND filing; its physical properties were investigated to improve its effectiveness and capability to form oral dosage forms. However, if such an approach were still not overcome, it would be dealt with at the subsequent level where a plausible process would begin. Thus, full-fledged preformulation development studies to deal with the issue were accomplished. The present review provides the recent advancements in both approaches to enhance dissolution rate and bioavailability of antihypertensive drugs.

Dissolution Process

The dissolution process is the complex physical phenomenon where the solid form of the drug is transitioned into solution form or homogenized in a dissolution medium resulting in its transparent solution. Compliance with the dissolution norm is mandatory to score better performances through bioavailability

enhancement. Though several theoretical principles concerning dissolution are proposed, i.e., Noye's Whitney theory is partially accepted, which explains precisely the process of drug dissolution. Still today, several academic modifications come forward to describe further the theoretical and practical knowledge emaciated in drug dissolution. According to these principles, the process of drug dissolution can be explained in the following series of events:

- Wetting of particle surface on the solid
- Breakdown of solid-state bonds
- Solvation of ions/entities
- Diffusion of solvated ions through stagnant layer
- Convective transport into the bulk medium.

Conventional Approaches

The development of pharmaceutical products with improved performance attributes, especially when dissolution, is much concerned since its active pharmaceutical ingredient (API) exhibits poor aqueous solubility. Poorly dissolvable antihypertensive drugs have been investigated to improve dissolution rates using various physical methods. Methods explored are broadly diversified, maybe using a size reduction approach, generation of new polymorphs of crystalline forms, or it could be the development of new binary or ternary dispersions,

- Solid-state changes: Polymorphism, Amorphous,
- Solid Dispersion: Binary/ ternary/ quaternary dispersion, polymeric/ surfactant dispersion
- Adsorption on mesoporous system
- Co-crystallization development
- Lyophilization, Co-grinding,

Milling/Grinding

It is the most convenient processing operation which can be easily scalable and industrially feasible though still practiced in conventional research and development. In this operation, the comminution of particulate solids has resulted, wherein a new surface in particulate solid is created. Grinding tangible results in creating the new surfaces in the solid per unit weight, allowing more contacts to form between dissolution fluids and new surfaces created. Conventionally, it is achieved when solid is passed through milling equipment and experiences various forces, e.g., multi mill or fluid energy mill. To improve the low solubility & bioavailability of poorly soluble drugs, nano or microcrystals were successfully prepared using a jet milling process. Processing using jet milling operation showed several-fold enhancement of poorly soluble drug oral bioavailability. Several modifications in the milling process showed that it had been explored to improve the dissolution enhancement of antihypertensive medications. It was reported that during cryomilling operation, crystalline forms of both drugs transformed into amorphous ones, as evidenced by the change in

the drug crystallinity. These findings significantly impacted the dissolution and bioavailability of drugs.

Modification in solid-state characteristics

Polymorphism is represented as the altered packing ability of a molecular entity where the drug atoms/ molecules are arranged in a spatial arrangement in the crystal lattice. Polymorphic research in product development is an integral part of preformulation studies where new physical forms of a drug with different solid-state characteristics are investigated. Developing a new polymorphic form of a poorly soluble drug is generally explored by harvesting a more contemporary crystalline form generated from solvent-mediated crystallization. For example, new crystalline forms of Telmisartan and Lisinopril dihydrate were reported with improved dissolution characteristics as a solubility function (Dinnebier R E et al., 2000; Sorrenti, M et al., 2013). Sometimes, the new polymorphic form is obtained through interconversion or from the transition of a crystalline state to the amorphous form of metastable structures (Zhou M et al., 2017).

Apart from conventional approaches utilizing, e.g., DSC, XRD, and FTIR methods, the crystal system can be easily assessed through SAXs, hot stage microscopy, or solubility studies in pharmaceutical systems. Generation of modified crystalline forms with changed characteristics is obtained when other excipients were intentionally added during the crystallization incorporation of gentisic acid and maleic acid into telmisartan results in improved dissolution rates(Haneef J et al., 2020). Co-crystallization of antihypertensive drugs with inert material can help to bring modification in drug dissolution rate. For example, the incorporation of xylitol as an inactive substance showed improvement in the dissolution rate of felodipine (Arafa M. F et al., 2018).

Chemical modifications

Another approach by which the drug solubility can be varied through chemical modification occurs in the basic structure. It can be carefully controlled through a decisive approach where a suitable salt of a drug is selected which can exist in the stabilized state at ambient temperature and humidity levels. Drug salts can be anionic or cationic HCl, HBr, Na, K salts, Choline, Hyclates, etc. Salt forming tendencies in antihypertensive have also been ascertained. Sodium and potassium salts of chlorothiazide were prepared and characterized. Salt formation is usually attributed to the chemical nature of the drug, relative stability of the drug, its pKa, crystallinity (Paluch K J et al., 2010; Paluch K J et al.,2011). Yet another industrially feasible approach that can be employed is chemically converting the poorly soluble drug into a somewhat soluble compound through the chemical esterification method. This method usually carried out in a suitable organic reaction results in the formation of esterified form, including maintaining the identity and purity of the drug.

Binary/ Ternary dispersion

The role of pharmaceutical additives is immensely critical in developing dosage form since each excipient is deliberately incorporated into the formulation and

has its contribution either in the stability, solubility, or processability of the drug product. Therefore it is always expected that each formulation additive confers its specific function in formulation design, specifically when there is a strong need to improve the poor dissolution rate. Therefore improvised formulation has been designed to include surface-active agents or similar substances like hydrophilic polymers to improve the drug dissolution behaviour. Surfactants are quantitatively measured in terms of their HLB values. Surfactant is added to bring out solubilization of a drug if its HLB is more balanced to give where drug molecules are solubilized. Usage of polymeric components in ternary dispersion systems immensely changed the drug dissolution behaviour. The possible role of polymeric components in the ternary dispersion is difficult to predict; however, some polymeric substances prevent the drug from undergoing a transition from soluble to a relatively less soluble state. Polymers and surfactants play essential roles in SDs by inhibiting precipitation caused by transitions from amorphous into crystalline form in supersaturated solutions and improving SD's physical stability (Franca M T et al., 2018).. The recent trend in ternary dispersion is given in the table. Polymers bring the supersaturation of drug in ternary dispersion leading to amorphization of the drug, presumably due to the hydrophobic interactions between the hydrophobic moieties of polymers and drug (Pui Y et al., 2018). The inclusion of a surfactant may result in more competitive interactions with polymers for drug molecules, as shown in Table 2.

Co-crystallization

Major bio-pharmaceutical issues concerning low solubility, poor dissolution rate, impaired permeability, or drug showed the first-pass metabolism improve the dissolution/bioavailability of poorly soluble drugs, including the Pro-drug approach, Salt synthesis, and Particle size reduction, Complexation, Change in physical form, Solid dispersions & Spray drying. Interactions responsible for forming co-crystals include hydrogen bonding, π- π-stacking, Van der Waals forces, and biodegradable hydrogel systems. Co-crystallization alters pharmaceutical material's molecular interactions and composition and is considered a better alternative to optimize drug properties. Pharmaceutical Co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability, and bioavailability in pharmaceutical development without changing the chemical composition of the API.

Solid State Adsorbtion

The present investigation's objective was to improve the dissolution characteristics of febuxostat, a BCS class – II drug, by formulating it as a solid dispersion adsorbate. Solid dispersion adsorbate(SDA) was prepared using labrasol, transcutol, and lutrol F127 as carriers and neusilin as adsorbent. The feasibility of hydrophilic silica aerogels as drug carriers and investigate the influence of the aerogel properties on the release rate of poorly water-soluble drugs. Hydrophilic silica aerogels of different densities were loaded with two model drugs, ketoprofen, and griseofulvin, by adsorption from their solution in supercritical CO2. The reasons for the release enhancement are the enlarged specific surface area of drugs by adsorption on aerogels compared to their

crystalline form and the immediate collapse of the aerogel network in aqueous media. The dissolution rate of poorly water-soluble drugs can be significantly enhanced by adsorption on highly porous hydrophilic silica aerogels.

Lipid-based delivery systems

These are new avenues in drug delivery systems in the recent investigations to challenge the problem of poorly soluble antihypertensives. These are the pre-concentrated mix consisting of oil, surfactant, drug, and cosolvent when agitated with externally aqueous medium transformed into oil in water dispersion. Suppose the dispersion resulted in the formation of a coarse emulsion. In that case, it becomes SEDDS. If whitish turbid admixture then becomes microemulsion (SMEDDS) or appearance of bluish or transparent dispersion upon addition of aqueous medium, it is denoted as nanoemulsion (SNEDDS). Formulation components in each system are selected based on higher drug solubility, the type of dispersion system sought, and the microemulsion/coarse emulsion region formation in ternary plots. Different lipid-based formulations of anti-hypertensive drugs like SEDDS, SMEDDS, and SNEDDS resulted in drug dissolution enhancement due to other mechanisms like micellization of surfactant, co-solvency effect, or nanoization of the oil droplets.

New Technologies

New technologies are widely explored to search for new investigational methods to successfully bring significant changes in the poor dissolution characteristic of drugs that belong to antihypertensive. Such technologies encompass the concepts of co-crystallization, generation and stabilization of amorphous form individually or in combination with other poorly soluble drugs. Besides the above, the latest technology includes a solid dispersion approach led by polymeric or phospholipids or surfactant combinations in binary or the ternary mixture, as shown in table 3, which were broadly described in the literature as shown in fig. 1.

Niche Technologies enhancing dissolution rate
Electrospinning (ES)

Electrospinning is a multifaceted process used to formulate nano or microfibers with desirable sizes and potentially drug delivery in a very controlled manner(Dzenis, Y. 2004). In the electrospinning method, a high voltage is applied over a polymeric solution or melt to induce charges in the solution, which is then forced out of the Taylor cone to form electrospun fibers. The formation of electrospun fibers has attracted attention because it provides a larger surface area where a larger amount of drugs can be incorporated. The high porosity and diameter variations can easily alter the drug's release kinetics. This method of generation of surfaces enhances the site-specificity, imparts good mechanical strength, biocompatibility, and biodegradation. One of the desirable features of electrospun nanofibres is that they can break down into fine fragments and easily degrade in the biological system, which cannot be achieved in other nanomaterials like nanoparticles. However, they are not easily biodegraded and removed from the body (as shown in fig. 2). A typical coaxial electrospinning system can be useful for fabricating core nanofibers to load many free drugs(Chen

H et al., 2008; Contreras-Cáceres R et al., 2019; Han D et al., 2019; Kenawy E R et al., 2002; Torres-Martínez E J et al., 2018).

Electrospun fibers arise as a potential drug delivery carrier as loading the drug is very easy, and the high voltage applied during preparation does not considerably affect the activity of the drug. Compared to bulk material like films, an electrospun fiber provides a larger release rate because of greater specific surface area and low diffusion path length. The release rate profile can be modulated as per requirement by altering the morphology of fiber, its porosity, and composition (Leuner C & Dressman J 2000). The therapeutic effectiveness of a therapeutic molecule relies upon the bioavailability and finally on the solubility of the drug molecules. Greater dissolution is one of the main characteristics necessary to obtain the required drug concentration in the systemic circulation. Unfortunately, around 40% of drugs in development and about 60% of active pharmaceutical ingredients obtained from synthesis have poor aqueous solubility. The problems related to the poor aqueous solubility of drugs are always the major concern during formulation development(Yu D G et al., 2018; Yang Y et al., 2019).

Li et al., in their research, fabricated carvedilol (non-cardioselective beta-receptor inhibitor antihypertensive) nanofibers by electrospinning process. The electrospun formulation can be utilized to impart all kinds of controlled release drug profiles like the immediate release(Wang K et al., 2018), sustained-release (Amarjargal A et al., 2019), delayed-release(Ma, K et al., 2019), on-demand release(Yang J et al., 2020),multiple-phase releases(Yu D G et al., 2020), and also controlled release of multiple components(Wei A F et al., 2011). It can be conveniently concluded that electrospun fabricated preparations can be a greater approach to overcome the dissolution-related challenges in the formulation development of antihypertensive drugs (Nguyen D N et al., 2016). Many biodegradable composite fibers of compound Antihypertensive Drugs (captopril and hydrochlorothiazide) by electrospinning technique. Their research work concluded that no chemical changes are observed in the drug component, which maybe because of the physical electrospinning process. Still, the drug lost its crystalline characteristics and became amorphous in the composite fibers as the process is very fast. Crystallization cannot take place in this short duration of time. It was also found that hydrogen bonds between drugs and polymeric carriers' formation lead to composite fibers' better heat stability (Kivikero N et al., 2009).

3D printing

Pills can be 3D imprinted in extraordinary sizes, shapes and with moderate delivery capacities. 3D printing likewise considers the modest production of the "polypill," A solitary pill can contain different medications that a patient is endorsed, decreasing the quantity of pills that should be devoured. The drug business is pushing forward at a fast speed. Present-day innovation has empowered the improvement of novel dose structures for designated treatment. Be that as it may, the manufacture of novel measurement structures at a mechanical scale is restricted, and the business actually runs on traditional medication conveyance frameworks, essentially changed tablets (Vithani K et al., 2019). The presentation of 3D printing innovation in the drug business has opened new skylines in the innovative work of written words and gadgets. The

primary advantages of 3D printing innovation lie in creating little groups of prescriptions, each with customized measurements, shapes, sizes, and delivery qualities. The production of prescriptions in this manner may at last prompt customized drugs to turn into a reality. This part outlines how 3D printed innovation has reached out from beginning unit activities to created eventual outcomes.

Co-Milling

Co-Milling is intended to decrease the size of applications. Co-Mill is intended for low warmth, low solid, low energy utilization activity, and speed variety. Particles tumble from the container into the plant's sharp edges, moving at an extremely high RPM. The effect of the edges on the particles is the reason for the estimating (Isaac J et al., 2016; Xiong X et al., 2019).

Freeze drying

Freeze-drying is a particular type of drying that eliminates all dampness and will generally have less impact on a food's taste than typical drying out does. In freeze-drying, food is frozen and set in a solid vacuum. Hence, freeze-drying is frequently saved for heat-delicate materials, like proteins, chemicals, microorganisms, and blood plasma. In addition, the low working temperature of the interaction prompts negligible harm to these delicate warmth items (Liapis A I & Bruttini R 2020; Wolkers W F et al., 2015).

Nanotechnology

Nanotechnology is being utilized in the field of drug dissolution rate enhancement for some reason. However, maybe the main objectives are to develop further drug solvency/bio-accessibility and conveyance to different locales of activity. Nanotechnology is additionally being utilized to foster better than ever helpful gadgets. Molecule size decrease shows up as a successful and adaptable alternative for dissolvability improvement. Nanonization is an appealing answer for work on the bioavailability of inadequately solvent medications, further developed treatments, in vivo imaging, in-vitro diagnostics, and the creation of biomaterials and dynamic inserts. Nanotechnology drug conveyance applications happen using planned nanomaterials just as framing conveyance frameworks from nanoscale atoms like liposomes. Applying nanotechnology to medicate conveyance ought to accomplish the accompanying advantages: Improve the capacity to convey inadequate water dissolvable drugs(Chen H et al., 2008; Dzenis Y 2004).

Nanosuspension technology

A drug nanosuspension is characterized as finely colloid, biphasic, scattered strong medication particles in a fluid vehicle, a size under 1 μm balanced out by surfactants and polymers arranged by reasonable strategies for drug conveyance applications. This plan addresses helpless water dissolvability, polymeric nanoparticles, parenteral nanosuspension, polymeric micelles, and arranged arrangement. Also, different procedures are utilized to improve the solvency of

inadequately dissolvable medications, including physical and substantial alterations of medications and different techniques like molecule size decrease, gem designing, salt development, strong scattering, utilization of surfactant, and complexation, etc. (Attari Z et al., 2016; Detroja C et al., 2011; Zhao J et al., 2016).

Mesoporous technology

Mesoporous nanoparticles have a strong system with a porous construction and enormous surface region, permitting the connection of various useful gatherings to focus on the medication moiety to a specific site. Artificially, MSNs have a honeycomb-like design and dynamic surface. As indicated by IUPAC terminology, a mesoporous material contains pores with distances across somewhere in the range of 2 and 50 nm. Microporous material is a material having pores less than 2 nm to 50 nm in length across. Mesoporous Silica as Carrier for Drug-Delivery Systems works on antimicrobial medicines productivity by planning new drug details displaying controlled delivery rate, designated conveyance, less incidental effects, and theranostic impacts.

Nanofibres technology

Nanofibres are generally characterized as round and hollow designs with an external measurement underneath 1,000nm and an angle proportion – the proportion among length and width – more noteworthy than 50. The distances across nanofibers rely upon the sort of polymer utilized and the strategy for creation. Nanofibers have numerous conceivable innovative and business applications. For instance, they are being used in tissue designing, drug conveyance, seed covering material, malignancy finding, lithium-air battery, optical sensors, and air filtration. The nanofibres/nanowires are traditionally characterized as one-dimensional nanomaterials, which normally have a measurement in the reach 1–100nm and the request for 1000nm or more (Farkas B et al., 2020; Shitole M M et al., 2020; Šrámková I H et al., 2019).

Solution Casting Method

The arrangement projecting strategy depends on the standard of Stokes' law. In this technique, polymer and prepolymer are similarly consolidated and make solvent in the appropriate format. The polymer is the lattice stage broke up effectively solvent in the arrangement, though the nanoparticles scattered in a similar structure or exceptional performance. In a film-projecting cycle, a trap of the thin film is expelled onto a chilled, profoundly cleaned, turning roll(Franca M T et al., 2018; Hörmann T R et al., 2018; Palazi E et al., 2018; Yeom D W et al., 2017). The speed of the roll directs the draw-down proportion and the thickness of the movie. The movie is then pulled by a stripping roll turning the other way to the projecting roll. To set up the polymer combination, unique arrangements of every polymer are planned (Fares A R et al., 2018; Shi X et al., 2019). In the first place, the polymers are broken down into toluene, and afterward, a blend with equivalent measures of every polymer is ready. The distinctive mode units contain a glass vial with an assorted combination of two polymers (Boyd B J et al., 2019; Torres-Martínez E J et al., 2018; Xiang T X et al., 2019).

pH Microenvironment Modulation

The balance of the microenvironmental pH could further develop the disintegration conduct of medications with pH-subordinate solvency, potentially prompting better oral ingestion. As per this idea, the balanced degree of microenvironmental pH and its span can be essential components for the development of drug disintegration. Those methods utilize certain presumptions and approximations, and large numbers of them use an answer adjustment bend of a test to anticipate hydrogen particle action in a generously dry strong. Despite the constraint of the technique, it is evident from the writing that microenvironmental pH fundamentally affects the strength of mixtures that show pH-subordinate solidness in the arrangement. Debasement energy of such mixtures and corruption profiles are now and again reliant upon the strong's microenvironmental pH. Therefore, adjusting the microenvironmental pH through pH modifiers can become an extremely successful apparatus in augmenting vital measurement structure dependability (Poudel S & Kim D W 2021). Microenvironmental pH tweak was likewise displayed to control the disintegration profile of both prompt and controlled delivery dose types of mixtures with pH-subordinate solvency. Moreover, pH modifiers were used in controlled delivery measurement types of feebly fundamental medications, showing lessened delivery in disintegration media with high pH. The consolidation of acidic pH modifiers in the controlled delivery plan builds the dissolvability of the essential medication even as the high pH disintegration medium goes into the measurement structure, subsequently expanding the medication discharge rate(Giri B R et al., 2021).

Gastro Retentive Drug Delivery System

Gastro retentive conveyance frameworks are intended to be held in the stomach for a drawn-out time frame and delivery their dynamic fixings, consequently empowering maintained and delayed contribution of the medication to the upper piece of the gastrointestinal (GI) plot. The oral course has been the most helpful and acknowledged course of medication conveyance. Attributable to the huge corrective advantages of the oral controlled delivery dose structures, the intriguing point regarding the drug field is accomplishing further developed therapeutics benefits (Karemore M N et al., 2019; Porwal A et al., 2017).

Hot-Melt Extrusion

Hot-melt extrusion (HME) was applied to foster nebulous robust scatterings. Generally, hot liquefy expulsion was a proficient system to upgrade the disintegration rate and oral bioavailability. Gastro retentive medication conveyance framework is an original medication conveyance framework that has the advantage because of its drawn-out holding capacity in the stomach(Hörmann T R., 2018; Xi L et al., 2018). Along these lines, it expands the gastric home season of medications and works on their bioavailability. This advertised arrangement and a few gastro retentive medication conveyance framework licenses address the coasting and non-drifting gastro retentive framework, which features a portion of the current gastro retentive methodologies(Ditzinger F et al., 2018; Vo A Q et al., 2017). Late ways to deal with incrementing the gastric home season of medication conveyance frameworks incorporate bioadhesive

frameworks, coasting frameworks (low-thickness frameworks), non-skimming frameworks (high-thickness frameworks), attractive frameworks, and growing, unfoldable and expandable frameworks, pontoon shaping frameworks, and very permeable frameworks, biodegradable hydrogel frameworks(Giri B R et al., 2021).

Quality by Designing

The strategy included the accompanying three stages: (1) hazard examination in distinguishing the material-and interaction related boundaries affecting the basic quality credits of disintegration testing, (2) an exploratory plan to assess the impact of configuration factors (traits and boundaries chosen by hazard investigation). (3) an examination of the connection between configuration elements and disintegration profiles. This examination applied the idea of Quality by Design (QbD) to tablet disintegration. Its objective was to propose a quality control technique to display disintegration testing of strong oral portion items per the International Conference on Harmonization rules. In addition, in light of the outcomes got, depicting disintegration is conceivable. The reasonableness and adequacy of the QbD approach were exhibited through this mechanical contextual analysis. Executing such a methodology deliberately in modern drug creation would lessen the requirement for tablet disintegration testing (Beg Set al., 2021; Prajapati P B et al., 2021; Arun J K et al., 2020).

3D Microprous Foam Technology

A three-dimensional (3D permeable metallic design ought to have a few critical advantages, including the accompanying: (I) Facile access of electrolyte to the anode surface, (ii) Facilitated charge move across the interface among cathode and electrolyte, (iii) Relieved weight on the crushing of dynamic material by giving void spaces to retain the vast volume changes, furthermore, (iv) High electron pathways in the terminal get together. Besides, a double pore-size and pore-shape dispersion engineering, interdigitated profoundly permeable metallic framework, can upgrade the volume thickness of dynamic material by expanding the surface space of the 3D platform as a format for stored dynamic material or as a functioning material itself. Three-dimensional permeable engineering makes an alluring terminal construction, as it has inborn underlying uprightness and a capacity to cushion pressure in lithium-particle batteries brought about by the enormous volume changes in high-limit anode materials during cycling. The primary showing of a SnO_2-covered macroporous Cu froth anode utilizes a versatile and straightforward blend of directional freeze-projecting and sol-gel covering measures. The three-dimensional interconnected anode is made out of adjusted microscale channels isolated by SnO_2-covered Cu dividers and considerably more fragile micrometer pores, adding to the surface region and giving space to volume development of the SnO_2 covering layer (Vithani K et al., 2019; Chung P et al., 2014; Šrámková I H et al., 2019).

Supercritical Fluid Technology

In a fast extension of supercritical arrangement (RESS), the supercritical liquid breaks down the solute to frame an answer. The rapid development of the performance happens across a fine spout or opening into the surrounding air.

Supercritical liquids have the exciting properties of acting like fluids and gases over their basic point. Supercritical liquid innovation has recently emerged as a green and novel procedure for different cycles, such as dissolvability improvement of inadequately solvent medications, plasticization of polymers, surface alteration, nanosizing, and nanocrystal change chromatographic extraction. Generally, audit/investigates having the benefits, negative marks, and different cycles like the quick extension of supercritical arrangements (RESS), particles from gas immersed arrangements (PGSS), gas antisolvent measure (GAS), supercritical antisolvent measure (SAS), and polymerization instigated stage detachment (PIPS), that have empowered this innovation to significantly raise the premium of scientists in the course of recent many years.

As of late arising innovation in the drug industry, the supercritical liquid invention uses supercritical liquids, which over their basic point show the exciting properties of fluids (dissolvable force, insignificant surface strain) just as gases (transport properties). This property has empowered supercritical liquids in creating extraordinary interest. The controlled medication molecule designing strategies, for example, shower drying, precipitation from supercritical liquid, controlled crystallization, enjoy the benefit of higher item yield, lower working temperature, and higher crystallinity of the powder with thin size appropriation. Subsequently, supercritical liquid procedure (SFT) can be utilized in the arrangement of better-designated conveyance to the lungs with further developed detailing attributes of the medication applicant, it helped atomization and CO_2 based airborne dissolvable extraction framework separately, and they may fill in as less firm, less agglomerated particles prompting more robust and reliable lung testimony (Pandya P A et al., 2020; Sodeifian G et al., 2020).

Electrospraying

The electrospraying or electrohydrodynamic atomization technique in the pharmaceutical application has been used over some past years. The particles can be produced at the nano or micro range with much more versatility, adaptability, and competency with desired structure, size, and shape, making it a prominent and preferred technique for pharmaceutical application. This method's desirability increases because of advantages like improved bioavailability of drugs with poor aqueous solubility, drug targeting systems, and controlled drug releasing approaches for delivering sensitive therapeutic agents like protein dependant drug-releasing approaches (Nguyen D N et al., 2016). Electrospraying produces micro or nano-scale particles with almost negligible accumulation because of their self-dispersing property. Different configurations like single, coaxial dual, or tricapillary nozzles can be used in the setup for the formulation of varied particles. The electrohydrodynamic principle can also be incorporated with techniques like fluid bed granulation(Kivikero N et al., 2009),

spray drying(Ho H & Lee J 2011), or inhalers. During drug administration, especially through the oral route, one of the crucial factors is the aqueous solubility directly related to the drug's effectiveness. Around 60% of the potential APIs have poor aqueous solubility, and they are categorized as Class II or Class IV under the biopharmaceutical classification system(Benet L Z et al., 2011). Poor dissolution rate and low aqueous solubility of active pharmaceutical ingredients

cause a decrement in bioavailability, retarded onset of drug action, and unpredictable absorption rate. It creates an issue with pharmaceutical preparations as many drug molecules get discarded in the initial phases of the formulation development. In past decades varied schemes like prodrug or salt development, usage of co-solvent, co-crystallization, formation of micro/nanoemulsions, reducing particle size up to the nanoscale and developing amorphous solid dispersions have been followed to resolve solubility related concerns of drugs to enhance the absorptivity and bioavailability (Singh A et al., 2011; Van Hoogevest P et al., 2011; Rabinow B E., 2004; Van den Mooter G.,2012). Even though all these approaches have shown some positive results, their disadvantages cannot be overlooked. All these methods are needed to process the specific properties of the drugs(Gao L et al., 2008). The poorly soluble API's get affected at the particulate level by using electrospraying or electrohydrodynamic atomization, producing the particles at the nanoscale and converting them into an amorphous state. The solution of the compound projected to electrospraying gets converted into fine droplets of micro or nano level by electrical forces, and instant solidification of these droplets is done by solvent evaporation. As the rapid process is used for evaporating the solvent, it initiates the amorphous state of the compound(Singh, A., & Van den Mooter, G. 2016; Paudel A et al., 2013). So, a presumption can be made that formulations prepared by the electrospraying technique anticipate improving the solubility of Class II and Class IV drug compounds as reduced or atomized size provides increased surface area higher free energy of drug in the amorphous state leads to improved dissolution (Farkas B et al., 2020).

Coaxial Electrospray

This examination writes about the original quick-dissolving centre shell composite microparticles of medication manufactured utilizing coaxial electrospraying. A covered concentric spinneret was created to lead the electrospray cycle. The pervasion rates across the sublingual mucosa are around multiple times quicker than simple API. Improving oral measurement structures containing ineffectively water-dissolvable medications is a critical test in the drug business (Yin, X et al., 2019). The innovation delivered centre shell particles made of medicines like quercitin, griseofulvin, and poly(methacrylic corrosive co-methyl methacrylate) (Eudragit L-100) a distance across of around 1 μm. The in-vitro disintegration and in vivo oral retention consider that the center shell definition fundamentally further progressive disintegration and ingestion practices, probably decreased molecule size, improvement in dispersity, and amorphization. The outcomes showed that coaxial electrospray statement has extraordinary potential as original plan innovation for upgrading oral ingestion of ineffectively water-dissolvable medications (Smeets A et al., 2020; Tanhaei A et al., 2020).

Conclusion and Perspectives

The emergence of recent technologies bringing out improved dosage forms/ delivery systems offer changes in the structure of poorly dissolvable antihypertensive and thereby modify its physical characteristics and attributes. These changes may be associated through amorphization of solid-state form or changes in crystal pattern; excipient mediated dissolution microenvironment,

surfactant linked solubilization or micellization, adsorption on the porous surfaces or generation of miniaturized size, Niche technologies and latest delivery system designing may functionalize independently or complementary. Still, its outcome enhanced the dissolution rate of poorly dissolvable antihypertensives to give new treatment modalities.

Acknowledgement

The authors are grateful to Chancellor Amity University, Noida, Uttar Pradesh, for providing various reprographic sources for implementing this work.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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Table 1
List of the drug belongs to the antihypertensive categories with potential bioavailability problems due to poor water solubility and intestinal permeability constraints

Category	Drug Examples	Ref.
Beta-blockers	Atenolol, Metoprolol	Moinuddin S M et al., 2017;

		Zhou M et al., 2017
ACE inhibitors	Ramipril, Lisinopril	Sorrenti M., 2013; Alhasani, K. F., 2019
Angiotensin II receptor blockers	Irebesartan, Candesartan, Azilsartan, Eprosartan	Verma R & Kaushik D., 2020
Calcium channel blockers	Amlodipine, Nifedipine, Diltiazem, Nicardipine, Verapamil	Lodagekar A et al., 2019
Alpha-blockers	Doxazosin, Prazosin	
Alpha-2 Receptor Agonists	Guanabenz, Guanfacine	Bolourchian N., 2019; Kajdič S et al., 2018; Singh B et al., 2013; Halder S et al., 2018
Combined alpha and beta-blockers	Labetalol, Carvedilol	
Diuretics	Furosemide, Indapamide	

Table 2
List of the drug depending upon nature becoming type polymeric dispersion

Dispersion former / Polymeric dispersion	Drugs	Nature	Ref.
Whey protein isolate/ Hydrolysate Carvedilol	Furosemide	Amorphous	Mishra J et al., 2019
PVP/PEG/Solupuls/kollidon	Felodipine	Molecular I	Palazi E N et al., 2018
PVP/ Eudragit/SoluPlus	Valsartan	Amorphous	Medarević D et al., 2018
HPMCE5/ Eudragit E	Nimodipine	Amorphous	Hörmann T R et al., 2018
HPC/HPMC	Felodipine	10 times sol	Vo A Q et al., 2017
Eudragit E 100	Lacidipine	Inhibitors	Sun M et al., 2017
His/Lys/Arg	Valsartan	Amorphous	Huang Y et al., 2017
Sodium Alginate	Telmisartan	Inhibitors	Borba P A A et al., 2016
Soluplus/PVP VA64	Lacidipine	Amorphous	Xi L et al., 2018
SLS/ Soluplus	Lacidipine	Amorphous	Guan J et al., 2019
PVP/SLS	Nimodipine	Amorphous	Pui Y et al., 2018

Soluplus/SLS	Chlorthalidone	6 times D	Franca M T et al., 2018
Sodium Alginate/ Soluplus	Chlorthalidone	Amorphous	Franca M T et al., 2018

Table 3
Technologies used to enhance the dissolution of antihypertensive drugs

Drug	BCS Class	Dissolution Enhancement	Ref.
Felodipine	II	Microparticule core-shell	Yin X et al., 2019
Telmisartan	II	Cubosomal tablet	Yasser M et al., 2019
Valsartan	II	Cocrystal with methyl paraben	Srivastava D et al., 2019
Candisartan	II	Cocrystal with methyl paraben	Srivastava D et al., 2019
Carvidilol	II	Stabilization of amorphous form	Mishra J et.al.,2019
Irbesartan	II	Nanocrystalline suspension	Meruva S et al., 2019
Valsartan-nifedipine	II	Co amorphousization	Lodagekar A et al., 2019
Carvidilol	II	Mesoporous silica nanoparticles	Li T et al., 2019
Lacidipine	II	Amorphous solid dispersion	Guan J et al., 2019
Lacidipine	II	Crystal growth inhibitor	Guan J et al., 2019
Olmesartan edoxomil	II	Nanocrystals	Chai R et al., 2019
Carvidilol	II	Ternary solid dispersion	Bolourchian N et al., 2019
Lacidipine	II	Amorphous solid dispersion	Xi L et al., 2018
Telmisartan	II	Phospholipid complexation	Son H Y et al., 2018
Nimodipine	II	Amorphous solid dispersion	Pui Y et al., 2018
Felodipine	II	Polymeric solid dispersion	Palazi E et al., 2018
Valsartan	III	Binary solid dispersion	Medarević D et al., 2018
Nimodipine	II	Silica nanoparticles	Li H et al., 2018
Carvedilol	II	Polymer nanofibers	Kajdič S et al., 2018
Nimodipine	II	Polymeric solid dispersion	Hörmann T R et al., 2018
Chlorthalidone	II	Polymer-surfactant dispersion	Franca M T et al., 2018
Valsartan	II	SMEDDS	Yeom D W et al., 2017
Felodipine	II	Amorphous solid dispersion	Vo A Q et al., 2017
Bosentan	II	SMEDDS	Vadlamudi H C et al., 2017
Lacidipine	II	Binary dispersion	Sun M et al., 2017
Atenolol-hydrochlorothiazide	II	Co-Amorphousization	Moinuddin S M et al., 2017
Telmisartan/ pravastatin	II	Ternary solid dispersion	Luo D et al., 2017
Valsartan	III	SNEDDS	Li Z et al., 2017
Valsartan	III	Co Amorphosization	Huang Y et al., 2017
Valsartan	III	Mesoporous silica nanoparticles	Biswas N et al., 2017
Valsartan	III	Semisolid SMEDDS	Zhao K et al., 2016
Nimodipine	II	Nanocrystals	Li J et al., 2016
Felodipine	II	Solid SMEDDS	Jing B et al., 2016
Telmisartan	II	Co-Polymer size-reduction	Isaac J et al., 2016
Valsartan	III	Nano sizing	Gora S et al., 2016
Telmisartan	II	Polymeric dispersion	Borba P A A et al., 2016

Valsartan	III	SNEDDS	Narayana L et al., 2015

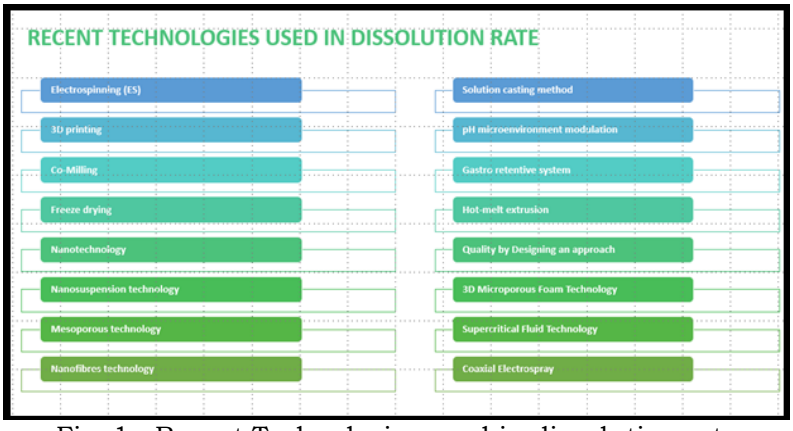

Fig. 1. Recent Technologies used in dissolution rate

Fig. 2. Machine used for Electrospinning