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The effect of particle size reduction on dissolution of ibuprofen

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ABSTRACT

The dissolution rate of a pharmaceutical drug is a critical factor in the design of effective oral dosage forms. Ibuprofen, a widely used oral medication, often faces challenges due to its inherently low dissolution rate. Traditional approaches to mitigate this issue involve increasing the dosage to enhance absorption and efficacy, thereby attaining the required therapeutic concentration. However, this solution can lead to various complications, including increased risk of side effects. This review examines alternative strategies to augment the dissolution rate of ibuprofen, with a specific focus on particle size reduction. Techniques such as salt and prodrug formation, crystal modification, micellar solubilization, complex formation, solid dispersion, and self-emulsifying drug delivery systems have been considered. The primary emphasis, however, is on the method of reducing particle size, an approach that has shown significant potential in improving ibuprofen's solubility. By enhancing the drug's solubility through particle size reduction, ibuprofen can be more readily absorbed, leading to improved therapeutic effectiveness without the need for increased dosages. This review aims to underscore the importance of particle size in drug design and its impact on the dissolution rate, offering insights into more efficient and patient-friendly ibuprofen formulations.

Keywords: particle size, dissolution, ibuprofen

Introduction

The evolution of drug preparations is a dynamic process, tailored to meet consumer demands and preferences. Pharmacists face numerous challenges in drug design and development, with poor drug solubility being a prevalent issue. The solubility of a drug is directly proportional to its dissolution rate, which is the rate at which a solid drug dissolves in gastrointestinal fluids. This dissolution is a critical factor to consider in the development of drug formulations, as it significantly impacts the drug's effectiveness [1].

The dissolution of drugs plays a vital role in determining their bioavailability in the bloodstream, which, in turn, influences the therapeutic effectiveness and treatment outcomes in patients. This relationship is particularly crucial in oral dosage forms, where the dissolution in water directly affects the absorption process. Consequently, the amount of the drug reaching the bloodstream is impacted [2]. Drugs that exhibit low dissolution rates are typically hydrophobic. When in the hydrophilic environment of the gastrointestinal tract, these substances tend to dissolve more slowly, adversely affecting both bioavailability and therapeutic efficacy [3].

Ibuprofen, classified as a class II drug in the Biopharmaceutics Classification System (BCS), exemplifies a drug with low solubility but high permeability [4]. Such drugs often exhibit inconsistent, slow, and incomplete absorption, necessitating formulation strategies to enhance solubility. Enhanced solubility ensures quicker release and absorption of the drug, leading to faster therapeutic effects [5].

To improve ibuprofen's dissolution, various methods have been explored. One widely employed strategy is the reduction of particle size [6]. By decreasing the size

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of drug particles, the surface area in contact with the dissolution medium increases, thereby enhancing the drug's absorption rate [7]. This article aims to explore the relationship between particle size and ibuprofen dissolution and to examine methods for reducing particle size. This inquiry is crucial in addressing challenges related to poor drug dissolution and in developing effective pharmaceutical preparations.

Drug dissolution of ibuprofen

Dissolution is the process whereby molecules detach from the surface of a solid drug and integrate into the solvent phase. This process is influenced by various intrinsic factors such as particle size, particle size distribution, surface area, crystal habit, and the solid-state properties of the substance. Extrinsic factors, including hydrodynamics and test conditions, also play a crucial role [8].

Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) commonly used for its analgesic and antipyretic effects, presents challenges in dissolution and tableting due to its hydrophobic nature [9]. Its solubility is notably low, measuring just 46.9 µg/mL at 37°C and 29.1 µg/mL at 25°C [10]. Given these solubility levels, enhancing the dissolution rate of ibuprofen is essential to improve its bioavailability in the bloodstream.

Effect of particle size on dissolution

The size and shape of particles play a crucial role in the manufacturing of solid dosage forms. Particle size impacts critical processes such as mixing, granulation, compression, and coating [11]. Furthermore, it influences the absorption rate and the drug dissolution process. Among the various methods to enhance dissolution, particle size reduction is the most commonly employed [6]. Decreasing the particle size increases the surface area in contact with the dissolution medium, thereby improving the drug's absorption rate [12].

In the quest to improve the dissolution of water-insoluble drugs, several studies have focused on converting these drugs into nanoparticle form. Nanoparticle dosage forms typically consist of solid substances with an average particle size ranging from 200-500 nm. This transformation into nanoparticles has been shown to improve the dissolution of ibuprofen [13].

A study by Hiendrawan et al. (2015) demonstrated that the rapid expansion supercritical solution (RESS) method significantly enhances the dissolution capability of ibuprofen. Ibuprofen particles not treated with RESS measured 48.549 ± 2.304 µm, while those processed with RESS were reduced to 3.765 ± 0.024 µm. The study revealed that the dissolution coefficient (kw value) of ibuprofen post-RESS treatment was 0.0495 min^{-1}, compared to 0.0277 min^{-1} for the untreated drug. This indicates that the dissolution rate of ibuprofen processed with RESS was approximately 1.79 times faster than that of untreated ibuprofen [14].

Methods of reducing particle size

Reducing particle size involves transforming large mass particles into smaller units or fine particles [15]. In the case of ibuprofen, which is available in forms such as tablets, suspensions, and injections, particle size reduction can be achieved through various modifications, both physical and chemical. Physical modifications include micronization and nanoization, co-crystallization, solid dispersion techniques, and cryogenic methods. Chemical modifications involve salt formation, pH adjustments, the use of adjuvants or surfactants, cosolvents, hydrotrophy, supercritical fluid processes, and self-emulsifying formations [4].

The techniques for particle size reduction can be broadly categorized based on the material's state. For solid materials, milling and cutting processes are used, whereas liquid materials are processed through emulsification or atomization. Factors such as hardness, toughness, rigidity, and moisture content of the material, as well as its melting point and abrasiveness, significantly affect the particle size reduction process [15].

Micronization

Micronization is a common method to improve solubility and dissolution rates of poorly soluble drugs. This process can be divided into top-down and bottom-up methods. Top-down methods, such as ball milling, jet milling, wet milling, and high-pressure homogenization, involve physical reduction of particle size [16]. Bottom-up approaches include removing particles from a solution via methods like supercritical fluid (SCF) technology, spray freezing, and evaporative precipitation [17].

High-pressure homogenization can effectively reduce particle size, with pressure application and cycle numbers being critical for optimal size reduction and preventing nanoparticle re-aggregation [18].

SCF processes, such as the RESS, supercritical anti-solvent (SAS), and particles from gas-saturated solutions (PGSS), are alternative micronization techniques. The RESS process is notable for its ability to control particle size, producing solvent-free nano or micro-sized particles [19]. This process involves dissolving the raw material in SCF, followed by rapid nucleation in a precipitation chamber, leading to fine particle formation. Optimal RESS conditions result in smaller, uniformly sized particles without altering the drug's crystallinity or chemical structure. Ibuprofen processed with RESS exhibits a notably increased dissolution rate [14].

Emulsification method

The emulsification method, which involves the use of polymers and cross-linking agents, is another technique for particle size reduction. Ionic gelation emulsification, in particular, has been effective in reducing ibuprofen particle size, thereby enhancing its solubility. This method involves creating a ibuprofen-PVA formula that produces fine white particles. The process includes a high-speed homogenization stage (5,000-10,000 rpm) where ibuprofen is broken into smaller globules [5]. This method is advantageous due to its simplicity, non-toxicity, room-temperature operation, adjustable size, and compatibility with macromolecular drugs [20].

Nanoization

Ultrasonication reduces particle size to the nanoscale by employing ultrasonic waves in the 20 kHz to 10 MHz frequency range, disrupting intermolecular interactions [21]. In ibuprofen's case, ultrasonication follows the dispersion process. The particles are initially formed through dispersion and then further reduced using ultrasonic waves, which create a strong cavitation effect in the solution, leading to the rupture of solution molecules [22]. Factors such as sonication time and wave intensity influence the uniformity and stability of the nanoparticles produced. Ibuprofen particles processed with ultrasonication are less than 300 nm in size and show enhanced dissolution compared to those produced by the ionic gelation emulsification method [23,24].

Freeze drying produces nanosuspensions with a higher release rate than the pure drug, especially when surfactants are added [18]. Spray drying, an alternative to milling, can reduce particle size and improve wetting by adding surfactants. When ibuprofen is spray-dried with gelatin and sodium lauryl sulfate, its dissolution rate in simulated gastric juices increases [25]. Spray drying typically yields amorphous particles, which have higher solubility and dissolution rates than crystalline forms [26]. Using poloxamer 127 as a surfactant in the spray drying of ibuprofen has been shown to enhance its dissolution [25].

Co-crystals

Cocrystals consist of two or more molecular or ionic compounds in a crystalline, single-phase material, often in stoichiometric ratios, excluding solvents or simple salts [27]. Common cocrystal formation methods include solvent evaporation, grinding, and solvent reduction [28]. For ibuprofen, cocrystals can be prepared using the solvent evaporation method with ibuprofen-nicotinamide in a 1:1 molar ratio, dissolved in ethanol. Nicotinamide's ability to form hydrogen bonds with ibuprofen's carboxylic acid groups leads to cocrystal compounds with improved dissolution rates [29].

The grinding method, also referred to as mechanical milling, involves crushing the coformer and active substance together, typically using a mortar and pestle. This technique has been applied to ibuprofen to form cocrystals by dry grinding with amino acid coformers like alanine, glycine, and proline. Notably, ibuprofen cocrystals formed with proline demonstrated increased solubility compared to pure ibuprofen, showcasing the effectiveness of this method [30].

Solid dispersion

Solid dispersion is a strategy employed to enhance the oral bioavailability of poorly soluble drugs. It involves creating a homogeneous mixture of one or more active pharmaceutical ingredients within an inert carrier matrix. This approach aims to reduce the particle size of the drug by forming a eutectic mixture with a water-soluble carrier, thus improving both solubility and absorption [31]. The effectiveness of solid dispersion largely stems from the reduced particle size and enhanced wettability of the drug [32]. In the case of ibuprofen, the utilization of PVP K90 as the dispersion matrix is critical. PVP K90 not only facilitates an increase in ibuprofen's dissolution rate but also enables the transformation of ibuprofen from a crystalline to an amorphous form, thereby improving

its dispersion in both solid dispersions and physical mixtures [33].

Conlusion

This review provides a comprehensive overview of various methodologies for reducing the particle size of ibuprofen, a widely used NSAID with inherent solubility challenges. Techniques such as ultrasonication, freeze drying, spray drying, co-crystal formation, and solid dispersion have been explored, each offering unique advantages in enhancing ibuprofen's dissolution rate. The findings underscore the importance of particle size reduction in improving the bioavailability of poorly soluble drugs. Ultrasonication and solid dispersion using PVP K90 have shown particular promise, indicating their potential as effective strategies for enhancing drug solubility and dissolution.

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References

1. Mehtani D, Seth A, Sharma P, Maheshwari R, Abed SN, Deb PK, et al. Dissolution profile consideration in pharmaceutical product development. Dosage form design considerations. Elsevier; 2018. pp. 287-336. https://doi.org/10.1016/B978-0-12-814423-7.00009-5
2. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines. 2022;10. https://doi.org/10.3390/biomedicines10092055
3. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021;26. https://doi.org/10.3390/molecules26195905
4. Singh AK, Chaurasiya A, Singh M, Upadhyay SC, Mukherjee R, Khar RK. Exemestane loaded self-microemulsifying drug delivery system (SMEDDS): development and optimization. AAPS PharmSciTech. 2008;9: 628-634. https://doi.org/10.1208/s12249-008-9080-6
5. Ferdiansyah R, Putri YD, Hamdani S, Julianto A. Peningkatan Kelarutan dan Disolusi Ibuprofen melalui Pembentukan Mikropartikel Metode Emulsification-Ionic-Gelation menggunakan Polivinil Alkohol (PVA) sebagai Polimer Tripolifosfat (TPP) sebagai Agen Crosslink. IJPST. 2018;4: 118. https://doi.org/10.15416/ijpst.v4i3.13864
6. Dizaj SM, Lotfipour F, Barzegar-Jalali M, Zarrintan MH, Adibkia K. Antimicrobial activity of the metals and metal oxide nanoparticles. Mater Sci Eng C Mater Biol Appl. 2014;44: 278-284. https://doi.org/10.1016/j.msec.2014.08.031
7. Dizaj SM, Vazifehasl Z, Salatin S, Adibkia K, Javadzadeh Y. Nanosizing of drugs: Effect on dissolution rate. Res Pharm Sci. 2015;10: 95-108.
8. D'Addio SM, Prud'homme RK. Controlling drug nanoparticle formation by rapid precipitation. Adv Drug Deliv Rev. 2011;63: 417-426. https://doi.org/10.1016/j.addr.2011.04.005
9. Rasenack N, Müller BW. Ibuprofen crystals with optimized properties. Int J Pharm. 2002;245: 9-24. https://doi.org/10.1016/S0378-5173(02)00294-6
10. Xu L, Li SM, Sunada H. Preparation and evaluation of Ibuprofen solid dispersion systems with kollidon particles using a pulse combustion dryer system. Chem Pharm Bull. 2007;55: 1545-1550. https://doi.org/10.1248/cpb.55.1545
11. Sabzevari A, Adibkia K, Hashemi H, Hedayatfar A, Mohsenzadeh N, Atyabi F, et al. Polymeric triamcinolone acetonide nanoparticles as a new alternative in the treatment of uveitis: in vitro and in vivo studies. Eur J Pharm Biopharm. 2013;84: 63-71. https://doi.org/10.1016/j.ejpb.2012.12.010
12. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian Journal of Pharmaceutical Sciences. 2014;9: 304-316. https://doi.org/10.1016/j.ajps.2014.05.005
13. Mansouri M. Preparation and Characterization of Ibuprofen Nanoparticles by using Solvent/ Antisolvent Precipitation. Open Conf Proc J. 2011;2: 88-94. https://doi.org/10.2174/2210289201102010088
14. Hiendrawan S, Veriansyah B, Tj RR, Rawinata. A bottom-up process approach for micronization of Ibuprofen. Journal of Chemical and Pharmaceutical Research. 2016;
15. Patel RP, Baria AH, Patel NA. An overview of size reduction technologies in the field of pharmaceutical manufacturing. Asian Journal of Pharmaceutics (AJP). 2008; https://doi.org/10.4103/0973-8398.45033
16. Verma S, Lan Y, Gokhale R, Burgess DJ. Quality by design approach to understand the process of nanosuspension preparation. Int J Pharm. 2009;377: 185-198. https://doi.org/10.1016/j.ijpharm.2009.05.006
17. Li X-S, Wang J-X, Shen Z-G, Zhang P-Y, Chen J-F, Yun J. Preparation of uniform prednisolone microcrystals by a controlled microprecipitation method. Int J Pharm. 2007;342: 26-32. https://doi.org/10.1016/j.ijpharm.2007.04.025
18. Nada A. Formulation of Ibuprofen Nanoparticles and Nanosuspensions with Enhanced Dissolution Rate using Ultra-Homogenization Technique. Asian Journal of Pharmaceutics (AJP). 2017;
19. Brion M, Jaspart S, Perrone L, Piel G, Evrard B. The supercritical micronization of solid dispersions by Particles from Gas Saturated Solutions using experimental design. J Supercrit Fluids. 2009;51: 50-56. https://doi.org/10.1016/j.supflu.2009.06.021
20. Mikušová V, Mikuš P. Advances in Chitosan-Based Nanoparticles for Drug Delivery. Int J Mol Sci. 2021;22. https://doi.org/10.3390/ijms22179652

21. Sulungbudi GT, Z.L. W, Salam R, Mujamilah M. Pengendalian suhu ultrasonikasi pada pelapisan nanopartikel magnet (fe3o4) dengan kitosan. J Kimia Kemasan. 2017;39: 95. https://doi.org/10.24817/jkk.v39i2.2838
22. Rusdiana IA, Hambali E, Rahayuningsih M. Pengaruh Sonikasi Terhadap Sifat Fisik Formula Herbisida yang Ditambahkan Surfaktan Dietanolamida. AGRORADIX : Jurnal Ilmu Pertanian. 2018;
23. Kemala T, Sjahriza A, Komariah S. Emulsi Dan Ultrasonikasi Dalam Pembentukan Nanoenkapsulasi Ibuprofen Tersalut Polipaduan Poli(Asam Laktat) Dengan Poli(ε-Kaprolakton). 2010;
24. Delmifiana B, - A. Pengaruh sonikasi terhadap struktur dan morfologi nanopartikel magnetik yang disintesis dengan metode kopresipitasi. Jurnal Fisika Unand. 2013;
25. Li DX, Oh Y-K, Lim S-J, Kim JO, Yang HJ, Sung JH, et al. Novel gelatin microcapsule with bioavailability enhancement of ibuprofen using spray-drying technique. Int J Pharm. 2008;355: 277-284. https://doi.org/10.1016/j.ijpharm.2007.12.020
26. Corrigan DO, Corrigan OI, Healy AM. Predicting the physical state of spray dried composites: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems. Int J Pharm. 2004;273: 171-182. https://doi.org/10.1016/j.ijpharm.2004.01.005
27. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury AR, et al. Polymorphs, salts, and cocrystals: what's in a name? Cryst Growth Des. 2012;12: 2147-2152. https://doi.org/10.1021/cg3002948
28. Jayasankar A, Somwangthanaroj A, Shao ZJ, Rodríguez-Hornedo N. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. Pharm Res. 2006;23: 2381-2392. https://doi.org/10.1007/s11095-006-9110-6
29. Agustin R, Sari N, Zaini E. Pelepasan Ibuprofen dari Gel Karbomer 940 Kokristal Ibuprofen-Nikotinamida. JSainsFarKlin. 2015;1: 79. https://doi.org/10.29208/jsfk.2014.1.1.15
30. Othman MF, Jamburi N, Anuar N, Abd. Rahim S, Rohalim NH. Ibuprofen-Amino Acids Co-Crystal Screening Via Co-Grinding Methods. MATEC Web of Conferences. 2016;69: 03002. https://doi.org/10.1051/matecconf/20166903002
31. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88: 1058-1066. https://doi.org/10.1021/js980403l
32. Barmpalexis P, Koutsidis I, Karavas E, Louka D, Papadimitriou SA, Bikiaris DN. Development of PVP/PEG mixtures as appropriate carriers for the preparation of drug solid dispersions by melt mixing technique and optimization of dissolution using artificial neural networks. Eur J Pharm Biopharm. 2013;85: 1219-1231. https://doi.org/10.1016/j.ejpb.2013.03.013
33. Retnowati D, Setyawan D. Peningkatan Disolusi Ibuprofen dengan Sistem Dispersi Padat Ibuprofen-PVP. Majalah Farmasi Airlangga. 2010;8: 24-28.