Review Article

An updated era on nanoparticle sustained release matrix tablets of NSAID using wet granulation technique

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How to cite this article:
Shinde SA, Kadam PS, Biradar MM, Tolsarwad GS. An updated era on nanoparticle sustained release matrix tablets of NSAID using wet granulation technique. Innov Pharm Pharmacother 2020;8(3):59-65.

Source of Support: Nil.
Conflicts of Interest: None declared.

ABSTRACT

Oral administration is the most convenient route among various routes of drug delivery as it offers high patient compliance. However, the poor aqueous solubility and poor enzymatic/metabolic stability of drugs are major limitations in successful oral drug delivery. There are several approaches to improve problems related to hydrophobic drugs. Among various approaches, nanotechnology-based drug delivery system (DDS) has the potential to overcome the challenges associated with the oral route of administration. Novel DDSs are available in many areas of medicine. The application of these systems in the treatment of hypertension continues to broaden. The present review focuses on various nanocarriers available in oral drug administration for improving solubility profile, dissolution, and consequently, bioavailability of hydrophobic antihypertensive drugs.

Keywords: Oral drug delivery, nanoparticles, wet granulation, matrix tablet

Introduction

Drug delivery systems

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues.[1] From this, new ideas on controlling the pharmacokinetics, Pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDSs), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects, and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery, and drug targeting systems are currently under development. Controlled and Novel/Modified Drug Delivery [Figure 1], which was only a dream or at bests, a possibility is now a reality. During the last decade and a half, pharmaceutical and other scientists have carried out extensive and intensive investigations in this field of drug research.[2]

Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH-or temperature-sensitive), and even targeted (e.g., by

Access this article online

Website: www.innpharmacotherapy.com
Doi: 10.31690/ipp.2020.v08i03.003
e-ISSN: 2321-323X
p-ISSN: 2395-0781

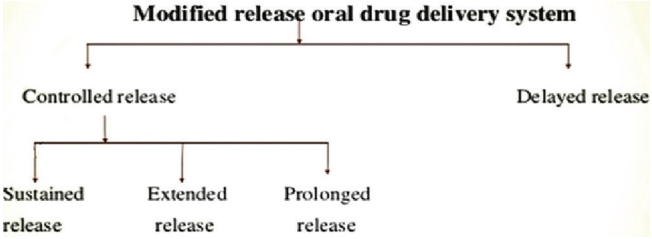

Figure 1: Classification of drug delivery systems

conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest.[3]

Novel drug delivery system

Although oral drug dosing is the most widely accepted route of administration, the gastrointestinal tract (GIT) presents several formidable barriers to drug delivery. Conventional oral drug administration does not provide a rate-controlled release. New drug delivery systems (NDDSs) have been successfully introduced throughout the 1980s and 1990s, mainly through the development of controlled release/sustained release oral delivery forms. A sustained release dosage form is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. NDDSs that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. The last two decades in the pharmaceutical industry have witnessed an avant-garde interaction among the fields of polymer and material science, resulting in the development of novel DDSs.[4] These new NDDS forms were mainly applied in the therapeutic areas of cardiac disorder, arthritis, smoking cessation, and chronic diseases or conditions that require continuous drug therapy for a long period of time. An additional advantage of this controlled release formulation is added economic value by enhancing the patient compliance, controlled drug input that prevents super- and sub-therapeutic plasma concentration, enabling targeting of drugs to the site of action, enabling a drug's release at the time when pharmacological action is indicated/needed and increasing comfort to the patient and improving health-related quality of life.[5]

Over the past few decades, there has been considerable interest in developing nanoparticles (NPs) as effective new oral drug delivery devices. Various polymers have been used in drug delivery research as they can effectively deliver the drug to a target site and thus increase the therapeutic benefit while minimizing side effects. The controlled release of pharmacologically active agents to the specific site of action at the therapeutic optimal rate and dose regimen has been a major goal in designing such devices. NPs generally vary in their size from 10 to 1000 nm. The drug is dissolved, entrapped, encapsulated, or attached to the NP matrix and depending on the method of preparation of NPs, nanosphere, or nanocapsules can be obtained.[6]

Oral route

Oral delivery is the preferred route of administration because it offers several advantages over other traditional routes such as intravenous and intramuscular injection. It is more natural, less invasive, can be self-administered (outside the hospital), and is less expensive.[7] For solid oral delivery systems, drug absorption is unsatisfactory and highly variable between individual despite excellent *in vitro* drug release pattern. The major problems are the physiologic variability such as variation in-transit time, variability in pH, and variability in the retention of dosage form. Even though the slow release occurs through the controlled release tablet but it is <12 h at the site of action.[8] This problem prompted the researchers to retain the DDS in the stomach more than 12 h. Such prolonged gastric retention time controls the time and space in stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug.[9] In pursuit of pulsatile release, various design strategies have been proposed, broadly categorized into single-unit and multiple-unit systems.[10] However, in recent pharmaceutical applications involving micro/NPs DDS are gaining much favor over single-unit dosage forms because of their potential benefits such as predictable gastric emptying, no risk of dose dumping, flexible release patterns, and increased bioavailability with less inter- and intra-subject variability.[9,10]

Recent developments in DDSs

Various DDSs, such as liposomes, micelles, emulsions, and polymer micro/NPs, facilitate application in controlled and targeted delivery.[11] The microencapsulation process in which the removal of the hydrophobic polymer solvent is achieved by evaporation has been widely reported in recent years for the preparation of polymeric micro/NPs. Micro/nanoparticulate DDSs have emerged as one of the most promising strategies to achieve site-specific drug delivery. The microencapsulation by the solvent evaporation method, high speed/pressure homogenization technique, and spray drying method is widely used in pharmaceutical industries. It facilitates a controlled release of a drug, which has many clinical benefits. Water-insoluble polymers are used as encapsulation matrix using this technique. The choice of encapsulation materials and the testing of the release of drug have been intensively investigated. Different kinds of drugs have been successfully encapsulated in biocompatible and biodegradable polymers. These are well-established technique, but it remains an active field of innovation, driven by the ever-increasing demand for more sophisticated particles.[12-15]

Microspheres/NPs have been prepared by various techniques, which feature partly competing, partly complementary characteristics. Many microencapsulation processes are modifications of the three basic techniques: Solvent extraction/evaporation, phase separation (coacervation), and spray-drying.[16]The solvent evaporation method has been used extensively to prepare poly (lactide) (PLA) and poly(DL-lactide-co-glycolide) (PLGA) microspheres containing many different drugs. Several variables have been identified which can influence the properties of the microspheres, including drug solubility, internal morphology, solvent type, diffusion rate, temperature, polymer composition and viscosity, and drug loading. Many types of drugs with different physical and chemical properties have been formulated

into polymeric systems, including anticancer drugs, narcotic agents, local anesthetics, steroids, and other fertility control agents.[12,17,18]

The solvent evaporation technique is fully developed at the end of 1970s. This classic technique convoluted by Bodmeier and McGinity, Ogawa *et al*., Jeffery *et al*., Iwata and McGinity, and different recent variations are commonly used for encapsulation of various substances from simple pharmaceutical products to protein and DNA.[19] Different kinds of drug were successfully encapsulated by the solvent evaporation technique.

Liu *et al*. successfully prepared relatively uniform-sized biodegradable PLA microcapsules with various sizes by combining a glass membrane emulsification technique and water-in-oil-in-water (w1/o/w2) double emulsion solvent evaporation method. The influence of process parameters on the size distribution of PLA microcapsules was investigated, with an emphasis on the effect of oil-soluble emulsifier.[20]

Saravanana and Anupama prepared ranitidine hydrochloride loaded floating microspheres by novel solvent evaporation-matrix erosion method using ethyl cellulose and polyethylene glycol (PEG) blend. PEG employed as a pore-forming agent to induce buoyancy. Drug loading, entrapment, and encapsulation of microspheres were 23–32, 86–96, and 75–86% (w/w), respectively. The average particle sizes were between 45 and 106 μm and reduced as % of PEG increases in the microspheres. Ethylcellulose microspheres prepared with 20–33.3% of PEG showed floating properties.[21]

Allen *et al*. showed that the addition of acetone to water at lower organic to aqueous phase ratio was an optimum procedure leading to higher drug encapsulation and smaller average diameter for the self-assembled structures.[22]

Sezgin *et al*.[23,24] investigate the solubilization of poorly water-soluble anticancer drugs, octaethylporphine, meso-tetraphenylporphine (mTPP), and camptothecin, in pluronic and PEG–distearoylphosphatidylethanolamine (DSPE) polymeric micelles. It was shown that drug loading efficiency highly depends on the polymer type, drug type, and their ratios. The most efficient drug loading was obtained by loading mTPP in PEG2000–DSPE and Pluronic F127 micelles. These results showed that besides their solubilizing effects, polymeric micelles could be useful as novel drug carriers for hydrophobic drugs. From the current number of studies being carried out by researchers all over the world, it is clear that release rates of microspheres depend on many possible factors.

Kwon *et al*.[25] describes the influence of preparation temperature on the various characteristics and release profiles of PLGA microspheres. The bovine serum albumin-loaded microspheres were prepared using the water-in-oil-in-water (w/o/w) technique with PVA as a surfactant in the external aqueous phase.[24,26] Microspheres' mean size increases and the particle size distribution widens with an increase in the preparation temperature.

Calija *et al*. investigated the feasibility of chitosan treated Ca-alginate microparticles for delivery of naproxen in lower parts of GIT and evaluated the influence of formulation factors on their physicochemical characteristics and drug release profiles. Investigated factors were drug/polymer ratio, chitosan molecular weight, chitosan concentration in hardening medium, and hardening time. Sixteen microparticle formulations were prepared utilizing 24 full factorial designs (each factor was varied at two levels).[27]

Zidan *et al*. deals with a case study to understand the effect of formulation variables of nanoemulsified particles of a model drug, cyclosporine A (CyA). A three-factor, three-level design of experiment with response surface methodology was run to evaluate the main and interaction effect of several independent formulation variables. This investigation demonstrated the potential of QBD in understanding the effect of the formulation variables on the quality of CyA self-nanoemulsified formulations. PLGA microparticles were prepared by developed single-phase oil in oil (o/o) emulsion solvent evaporation technique. Insulin, a model protein, was successfully loaded into microparticles by changing.[28]

Hamishehkar *et al*. showed that the encapsulation efficiency of insulin was mainly influenced by surfactant concentration. Moreover, polymer concentration and polymer molecular weight affected the burst release of drug and size characteristics of microspheres, respectively. It was concluded that using PLGA with higher molecular weight, high surfactant, and polymer concentrations led to a more appropriate encapsulation efficiency of insulin with low burst effect and desirable release pattern.[29]

Liu *et al*. were studied the factor influence of pulsed frequency, binder spray rate, and atomization pressure of a top-spray fluidized bed granulation process using the Box–Behnken experimental design method. The study has supported the theory that the granule size can be controlled through the liquid feed pulsing. Various researchers studied the solvent evaporation method for the encapsulation of drug in polymeric micro/NPs.[20]

Cheong *et al*. studied a top-down approach based on the emulsification evaporation technique to prepare nanodispersion of α-tocopherol. The results showed that homogenization pressure has a significant ($P < 0.05$) influence on the droplet diameter and size distribution. On the contrary, the processing cycle had not significant ($P > 0.05$) effect on the droplet diameter and size distribution of the prepared nanodispersion. Droplet diameters in the range of 90–120 nm were obtained for the prepared α-tocopherol nanodispersions. During storage duration, there were no significant ($P > 0.05$) changes in mean diameters, while the concentrations of α- tocopherol were significantly ($P < 0.05$) reduced for all prepared nanodispersions.[30]

Dong and Feng employed high-pressure homogenization to prepare PLGA NPs for the controlled release of paclitaxel. The drug encapsulation efficiency ranged from 34.8 ± 1.6 to 62.6 ± 7.9%, depending on the homogenization pressure and cycles. Paclitaxel was released from the NPs in a biphasic profile with a fast release rate in the first 3 days followed by a slow first-order release.[31]

Bhavsar *et al*. reported the encapsulation of fluorescein isothiocyanate-labeled gelatin NPs into polycaprolactone microsphere

(NP-in-microsphere oral delivery system, NiMOS) by double emulsion like technique and the influence of variables such as polymer concentration in the organic phase, amount of NPs added as internal phase and the speed of homogenization on the particle size of NiMOS using a 33 randomized full factorial design. The results from multiple linear regression analysis and Student's t-test revealed that for obtaining large particles of NiMOS, a high polymer concentration and low speed of homogenization was necessary.[32]

To improve the water solubility, Ohshima *et al*. prepared nifedipine-lipid NP suspensions by a combination of co-grinding by a roll mill and high-pressure homogenization without any organic solvent. The mean particle size and zeta potential of the nifedipine-lipid NP suspensions were about 52.6 nm and −61.8 mV, respectively, and each parameter remained extremely constant during a period of 4 months under 6°C and dark conditions, suggesting that the negative charge of the phospholipid, dipalmitoylphosphatidyl glycerol, is very effective in preventing coagulation of the particles.[33]

Budhian *et al*.[34] produced haloperidol-loaded PLGA/PLA NPs using two emulsification-solvent evaporation methods: Homogenization and sonication. The interdependencies between processing and materials parameters and the subsequent NP characteristics are discussed in terms of underlying scientific principles that are broadly applicable to the production of drug-loaded polymer NPs. This level of understanding should quicken the pace of designing protocols for making new drug-PLGA NPs. It was determined that the particle size of haloperidol-loaded PLGA/PLA NPs is effectively controlled by the amount of shear stress transferred from the energy source to the organic phase, which is strongly correlated to the following parameters: Type of applied energy, aqueous phase volume, and polymer concentration in the organic solvent.

Sustained Release Drug Delivery

Sustained release is defined as the delivery of drug as an initial (loading) dose immediately and the loading dose is followed by a slow constant release. It is the DDS that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. By the sustained release method, therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of the patient. Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues.[35] For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which, in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu, and absorption through an epithelial membrane to the blood. In this review, we discussed the sustained DDS.[36]

Advantages

1. Reduction in drug plasma level fluctuations.
2. Maintenance of a steady plasma concentration of the drug over a prolonged time period, simulating an intravenous infusion of a drug.
3. Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release.
4. Dosage forms, greatly reducing the possibility of side effects, which increases as we approach the MSC.
5. Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.[36]

Disadvantages

1. Stability problem.
2. Toxicity due to dose dumping.
3. Increased cost.
4. More rapid development of tolerance.
5. Need for additional patient education and counseling.
6. Reduced potential for dosage adjustment of drugs normally administered in varying strength.[36]

The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, and providing uniform drug delivery. The sustained release system is a type of modified DDS that can be used as an alternative to conventional DDS. These systems sustain the release of drug and maintain the plasma drug concentration in the therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in the therapeutic window. Sustained release systems have benefits such as patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects, and overcome the problems associated with the conventional system; oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as the design and testing of products.[37]

NPs

NPs and nanostructured materials represent an active area of research and a techno-economic sector with full expansion in many application domains. NPs have gained prominence in technological advancements due to their tunable physicochemical characteristics such as melting point, wettability, electrical and thermal conductivity, catalytic activity, light absorption, and scattering, resulting in enhanced performance over their bulk counterparts. A nanometer (nm) is an International System of Units (Système international d'unités, SI) unit that represents 10−9 meter in length.[38] In principle, NMs are described as materials with a length of 1–1000 nm in at least one

dimension; however, they are commonly defined to be of diameter in the range of 1 to 100 nm. Today, there are several pieces of legislation in the European Union (EU) and USA with specific references to NMs. Applications of NPs in several research areas are shown in Table 1.

However, a single, internationally accepted definition for NMs does not exist. Different organizations have a difference in opinion in defining NMs. According to the Environmental Protection Agency, "NMs can exhibit unique properties dissimilar than the equivalent chemical compound in a larger dimension." The US Food and Drug Administration also refers to NMs as "materials that have at least one dimension in the range of approximately 1–100 nm and exhibit dimension dependent phenomena."[39] Similarly, The International Organization for Standardization (ISO) has described NMs as a "material with any external nanoscale dimension or having internal nanoscale surface structure." Nanofibers, nanoplates, nanowires, quantum dots, and other related terms have been defined based on this ISO definition. Likewise, the term nanomaterial is described as "a manufactured or natural material that possesses unbound, aggregated or agglomerated particles where external dimensions are between 1 and 100 nm size range," according to the EU Commission.[40]

Preparation of oral solid dosage forms (tablets) from NPs

There have been increasing interests for drug companies to incorporate drug NPs into their existing formulations. However, technical knowledge in this area is still in its infancy and more study needs to be done to stimulate growth in this fledgling field. There is a need to scrutinize the performance of pure drug NPs in tablets, particularly relating formulation variables to their dissolution performance. Application of the pure form, synthesized without the use of surfactants or stabilizers, is often preferred to maximize drug loading and also to minimize toxicity. The main hurdle confronting the effective use of pure drug NPs in tablets is the difficulty in controlling aggregation in solution, which could potentially be aggravated by the tableting process.[41]

Dissolution rate enhancement of drug includes solid dispersion with polyvinylpyrrolidone K25,[42] hot-melt extrusion with hydroxypropyl cellulose and PEG, and inclusion complexes with beta-cyclodextrin and hydroxypropyl beta-cyclodextrins. However, these approaches have met limited success. Several other general techniques have been developed to enhance the dissolution rate of poorly water-soluble drugs. Such methods include solubilization by salt formation.[43] The solubilization technique by salt formation is a complicated process and is not feasible for a compound that does not have ionizable groups. An approach that is commonly used to increase dissolution velocity and impact saturation solubility of sparingly soluble compounds is to formulate it as nanometer-sized particles, particles usually <1 μm in diameter. For example, when the particle size of the drug is reduced from 8 μm to 200 nm, there is a 40-fold increase in the surface area to volume ratio. This increase in surface area can provide a substantial increase in the dissolution rate if the formulation disperses into discrete particles.[44]

Table 1: Applications of nanoparticles in the field of sustained drug delivery

Application in drug delivery	Example
To reduce side effects 5	Fluorouracil
To reduce drug toxicity doxorubicin	Dehydroemetine
To enhance therapeutic index doxorubicin	To enhance therapeutic index doxorubicin
To improve/enhance bioavailability vincamine	Avarol
For prolonging drug action insulin	Influenza whole virus
To improve stability influenza vaccine	To improve stability influenza vaccine
For controlled-release theophylline	Calcitonin
For targeting phthalocyanines and napthalocyanines	Monoclonal antibodies
Investigational and miscellaneous	Lactam antibiotics, cyclosporin

Wet granulation technique

Granulation, the process of particle enlargement by agglomeration technique, is one of the most significant unit operations in the production of pharmaceutical dosage forms, mostly tablets and capsules. Granulation process transforms fine powders into free-flowing, dust-free granules that are easy to compress. Nevertheless, granulation poses numerous challenges due to the high-quality requirement of the formed granules in terms of content uniformity and physicochemical properties such as granule size, bulk density, porosity, hardness, moisture, and compressibility together with the physical and chemical stability of the drug. Granulation process can be divided into two types: Wet granulation that utilizes a liquid in the process and dry granulation that requires no liquid. The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow, and release properties, to name a few. Among currently available technologies, spray drying, roller compaction, high shear mixing, and fluid bed granulation are worth of note. Like any other scientific field, pharmaceutical granulation technology also continues to change, and arrival of novel and innovative technologies is inevitable. This review focuses on the recent progress in the granulation techniques and technologies such as pneumatic dry granulation, reverse wet granulation, steam granulation, moisture-activated dry granulation, thermal adhesion granulation, freeze granulation, and foamed binder or foam granulation. This review gives an overview of these with a short description about each development along with its significance and limitations.[10]

Wet granulation has seen many technical and technological innovations as compared to dry granulation. Molecules that need wet granulation are those not suited for dry granulation process – high dose, poor flow, low in bulk density, and without binding properties.

Wet granulation is a widely used technique that produces granules through wet massing of the active pharma ingredient and granulation liquid with or without a binder. Wet granulation is carried out in two ways – one method is to moisten the powder or powder mixture and pass it through a screen of the mesh size needed to produce granules in the desired size using dry heat. The second type used a fluid bed

processor in which particles are placed and vigorously dispersed and suspended while liquid excipient is sprayed onto the particles and dried. Depending on molecule sensitivity, aqueous (water) or non-aqueous (organic) solvents are used for the granulation process. Aqueous processes are considered safer and cost-effective.[45]

Conclusion

Nanotechnology holds great potential in the effective delivery of poorly soluble NSAID drugs by improving solubility and oral bioavailability and hence can play a crucial role in developing sustained-release formulations.

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