ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Novel technologies for oral delivery of poorly soluble drugs

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ABSTRACT

The preferred route of oral administration is limited to those drug molecules that are permeable across the gastric mucosa and are at least sparingly soluble. A large majority of the new chemical entities and many existing drug molecules are poorly soluble, thereby limiting their potential uses and increasing the difficulty of formulating bioavailable drug products. There are numerous methods that may facilitate solubility to further enhance performance of poorly soluble drugs for oral administration – several of the older technologies i.e. size reduction via comminution and spray drying. Other techniques are inclusion complexes, cyclodextrin complex, microemulsion and self emulsifying system, solubilizing excipients, use of surfactants, pH modifications and solid dispersions. These all technologies have been used to overcome the solubility problems but, the novel technologies have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages.

Keywords: Poorly soluble drugs, supercritical fluid, nanocrystal, sono-crystallisation

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ISSN: 0975-8585

INTRODUCTION

Over the last ten years the number of poorly soluble drugs has steadily increased. It is estimated that 40% of the drugs produced by the pharmaceutical companies or industries have solubility problems [1]. By studying the literature, it states that 60% of all the drugs synthesized are now a day poorly soluble [2]. Poor solubility in water correlates with poor bioavailability. If drug solubility is not improved, then it will not be able to be absorbed from the gastrointestinal tract into the bloodstream and reach the site of action [3]. Drug solubility in the aqueous environment of the gastrointestinal (GI) tract is one of the primary factors influencing the rate and extent of drug absorption and therefore determining the overall bioavailability, but also impacts other pharmaceutical properties such as speed of onset of action and fed/fasted variation.

It is very much difficult to bring a new chemical entity (NCE) in the market. It takes to much cost *i.e.* $897 million, on average **[**4] or nearly doubles to $1.7 billion when you factor in the costs of failed prospective drugs and nearly about 10 to 20 years. Of all the NCE's created through R&D process, only about 10% make it through to receive market approval. For this reason many potentially promising drugs never make it to market or are developed in sub-optimal formulations. This is not good for pharmaceutical companies who have been facing a growing R&D productivity crisis in recent years, nor does it help patients whose quality of life might be improved if these candidates were developed rather than dropped due to their poor biopharmaceutical properties [5].

So, there are varieties of techniques have been studied to enhance the solubility of poorly soluble drugs. First of all it should be decided whether a particular drug can be solubilized to a specified extent and if so then what technique of solublization will be most effective. To solve the problems of absorption of poorly soluble drugs, various recent novel techniques such as particle size reduction via sonocrystallisation, super critical fluid (SCF), micronisation via nanoparticle nanoemulsion, nanosuspension, spray freezing into liquid, commercialized nanotechnologies biorise technology, diffucap's technology and Do-coops technology have been reviewed in this article. These novel technologies can be utilized for oral delivery of hydrophobic drugs.

SONOCRYSTALIZATION

Recrystallization of poorly soluble material using liquid solvents and antisolvents has also been employed successfully to reduce particle size [6]. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is sonocrystallization. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. It not only enhances the nucleation rate but also an effective means of size reduction & controlling size distribution of the active pharmaceutical ingredient (A PI) [7]. Most applications used ultrasound in the range 20khz-5mhz17 [8].

Sonocrystallization technique or technology has also been studied to modify the undesirables of NSAID'S (flubiprofen) *i.e.* poor solubility and dissolution rate and consequently the poor bioavailiability. Flubiprofen was poured in deionized water at 25°C and sonicated for 4 minutes at an amplituted of 60% and cycle is 40 sec on and 10 sec off. The particle size of treated flubiprofen was significantly reduced and the increased solubility of treated flurbiprofen was about 35%. The intrinsic dissolution rate of treated flubiprofen increased by 2-fold. The dissolution studies obtained that 90% of the drug was released within 20 minutes for treated flubiprofen as compared to untreated flubiprofen obtained 60% release of the drug [9].

SUPERCRITICAL FLUID PROCESS

Another novel nanosizing and solublization technology whose application has increased in recent year is particle size reduction via supercritical fluid processes [10]. A supercritical fluid (SCF) is a substance whose temperature and pressure are simultaneously above its critical point. At critical point, critical temperature is the temp above which the substances can no longer exists as a liquid no matter how much pressure is applied and critical pressure is the pressure above which the substances can no longer exists as a gas no matter how much temperature is applied. SCF liquids have solublizing nature. Gases have diffusivity and compressibility/expandable nature. Super critical fluid offers liquid like density and solublizing capacity, gas like viscosity, compressibility and diffusivity allowing for good mixing and mass transfer hence, labeled as fluids. SCF offer tremendous potential, as it is safe, inexpensive, ecofriendly, non-toxic and economical. With SCF's at hand, there is no need of any organic solvent. Once the drug particles are solubilized within SCFs, they may be recrystallized at greatly reduced particle size.

A SCF process allows the micronization of drug particles within sub micron levels. Current SCF process had demonstrated the ability to create nanoparticulate suspension of particles 5 to 2000nm in diameter [11]. The most widely employed methods of SCF processing for micronized particles are rapid expansion of supercritical solutions (RESS) and gas antisolvents recrystallization (GAS), both of which are employed by the pharmaceutical industry using carbon dioxide (CO_2) as the SCF [12].

RESS

This process is applicable to the substances those are soluble in supercritical fluids. In this process, first the solute is dissolved in a supercritical fluid then it is passed through a nozzle at supersonic speed. Pressure reduction of solution in a nozzle leads to a rapid expansion. This RESS leads to super saturation of the solute and subsequent precipitation of solute particles with narrow particle size distributions [13]. Pathak *et al.,* 2004 applied SCF processing technique *i.e.* rapid expansion of super critical solution in a liquid solvent (RESOLV) for the nanosizing of water insoluble drug particles. The drugs used for nanosizing were anti-inflammatory Ibuprofen and Naproxen for which CO_2 and CO_2–co solvent system were used due to its favorable processing characteristics' like its low critical temp (T_C=31.1-C) and pressure (P_C=73.8 bar). The RESOLVE process produced exclusively nanoscale (less than 100nm)

Ibuprofen and Naproxen particles suspended in aqueous solution and the aqueous suspension of the drug nanoparticle are protected from agglomeration and precipitation by using common polymeric and oligomeric stabilizing agents although particles are obtained by the RESS recently nanometric particles production has been reported in most cases micrometer and sub micrometer sized [14].

GAS

This processing requires drug polymer mixture be solubilized via conventional means into a solvent *i.e.* then sprayed into an SCF, the drug should be miscible with the organic solvent. The SCF diffuses into the spray droplets, causing expansion of the solvent present and precipitation of the drug particles. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry [15].

Solution Enhanced Dispersion with Supercritical Fluids (SEDS)

This technique was developed at the University of Bradford to overcome some of limitations of the RESS and GAS the drug solution & the SCF are introduced simultaneously in to the particle formation vessel using a co-axial nozzle arrangement. It causes rapid dispersion, mixing &extraction of the solvent by SCF leading to very high super saturation resulting in precipitation.

Super critical assisted atomization (SAA)

It was developed to produce microparticles of new asthma controlling drug. It was proposed an alternative to conventional jet-milling process the effect of this SAA was evaluated on morphology & size of precipitated particles SAA were produced the spherical particles with mean size ranging from 1 to 3 µ of the new anti-asthma drug. By using the SAA technique the mass median aerodynamic diameter (MMAD) of this technique & the conventional technique was compared, particularly, MMADS from 1.6 to 4.0 µm were obtained by SAA at the optimum operating conditions & MMAD of 6.0 µm was calculated for the conventional jet-mill drug. SAA also exhibited narrow particle size distribution (PSD), so it was shown that a good control of particle size was developed by SAA process and no degradation was obtained this novel technology for microparticles preparation of an asthma controlling drug [16].

Several other methods of SCF processing have been developed such as precipitation with compressed antisolvent process (PCA), super critical anti solvent process (SAS) and aerosols super critical extraction system (ASES) aerosol solvent extraction system (ASES) to produce micro particles drug and polymer are to be dissolved /dispersed in an organic solvent and sprayed through a nozzle into the column with super critical gas phase the rganic miscible with the super critical gas phase will be extracted resulting in the formation of solid micro particles.

ISSN: 0975-8585

NANOTECHNOLOGY

Nanotechnology will affect our lives over the next decade in every different field including medicine & pharmacy. Transfer of material in to nanodimension changes their physical properties which were used in pharmaceutics to develop new innovative for poorly soluble drugs [1]. The delivery of poorly soluble drugs into the body in a sufficiently bioavailable form has been challenging for formulation researchers, especially if a drug also is insoluble in an organic medium. Although several approaches such as solublization [17,18] co solvency(19) complexation with beta-cyclodextrin [20,21] and solid dispersion [22-24] can enhance a drug's dissolution, these methods are limited and suffer from disadvantages such as environmental concerns (*e.g.,* because of the need for organic solvents), low drug loading, and large doses.

In the recent years, nanoparticle technology has emerged as a strategy to tackle such formulation problems associated with poorly water-soluble and poorly water and lipid-soluble drugs (25, 26-28). Nanoparticles are solid colloidal particles ranging in size from 1 to 1000 nm that are used as drug delivery agents. (29) The reduction of drug particles to the nano-scale increases dissolution velocity and saturation solubility, which leads to improved *in vivo* drug performance (30, 31). The various advantages of formulating water-insoluble drugs as nanoparticle are provided in the sidebar, "Benefits of pharmaceutical nanoparticle"(32-36). Nanoparticles can be produced by either dispersion-based processes (which involves breaking larger micrometer-sized particles into nanoparticle) or precipitation-based processes (which involves nucleation of particles from the molecular state). Nanoparticle production processes should be simple, continuous, and efficient, viable for large-scale production, should effectively screen out most micronized particles and be acceptable to regulatory authorities. Nanotechnology requires flexible amounts of drug and processes such as wet milling, high-pressure homogenization, emulsification, precipitation, rapid expansion, and spray freezing can be used to produce drug nanoparticle.

Nanosuspension Technology

Nanosuspension technology offers novel solution for these poorly soluble drugs. Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. Nanosuspension differ from nanoparticle, which are polymeric colloidal carriers of the drug and solid lipid nanoparticle, which are lipidic carrier of the drug and solid lipid nanoparticle, which are lipidic carrier of drug. The poorly soluble drug and low bioavailable drug so called “brick dust” candidate once abandoned from formulation development can be rescued by formulating in to nanosuspension. Nanosuspension technology offers solution not only to solubility of drug but also alters the pharmacokinetic of drug and thus improves the safety & efficacy [37]. Alternatively, the nanoparticle suspension can be obtained by diluting an emulsion prepared by conventional methods, which results in the complete diffusion of the internal phase into the external phase leading to nanoparticle suspension. By forming drug nanosuspension using emulsification technology, the mitotane anticancer drug dissolution rate was increased by five-fold compared with commercial products (38).

The use of micro emulsion as templates for producing drug nanosuspension also has been reported in literature. The dissolution rate of the antifungal Griseofulvin drug was enhanced three-fold compared with the commercial products by formatting a nanosuspension using micro emulsion (39). Emulsification technology cannot be used for drugs that are poorly soluble drugs in both aqueous and organic media. Moreover, the use of organic solvents also poses environmental concerns. It is clear that when a drug forms insoluble complex than take an advantage of nanosuspension technology [37].

Nanoemulsion Technology

Nanoemulsions are submicron sized emulsions that are under extensive investigation as drug carriers for improving the delivery of therapeutic agents. They are by far the most advanced nanoparticle systems for the systemic delivery of biologically active agents for controlled drug delivery and targeting. Nanoemulsion are the thermodynamically stable isotropic system in which two immiscible liquid (water and oil) are mixed to form a single phase by means of an appropriate surfactants or it mix with a droplet diameter approximately in the range of 0.5-100 um. Nanoemulsion droplet sizes fall typically in the range of 20-200 nm and show narrow size distributions [40]. Nanoemulsions are prepared by the spontaneous emulsification method (titration method). They can be prepared simply by blending oil, water, surfactant, and cosurfactant, in the right proportion, with mild agitation. The order of mixing the components is generally considered not to be critical since nanoemulsions are formed spontaneously. Although nanoemulsification is a spontaneous process, the driving forces are small and the time taken for these systems to reach equilibrium can be long [41]. Tiwari S B *et al.,* prepared Paclitaxel nanoemulsion by sonication method and characterized for particle size & surface charge .The results obtained by this formulation had a particle size range of 90-120 nm & zeta potential ranging from+34mV to -45mV. Following the oral administration, a significantly higher concentration of Paclitaxel was observed in the systemic circulation. Formulation of nanoemulsion were shown to generate enhancement in the oral bioavailaibility of Paclitaxel, relative to administration in aqueous solution, the results of this drug suggests that nanoemulsion are promising novel formulation that can enhance the oral bioavailability of hydrophobic drug [42]. It was also observed that the dissolution of poorly soluble drug, Celecoxib (CXB) was enhanced by nanoemulsion techniques [43].

Spray freezing in to liquid (SFL)

In this process, developed at the University of Texas at Austin (Austin, TX) and commercialized by Dow Chemical Company (Midland, MI), an aqueous, organic, or aqueous–organic co solvent solution; aqueous–organic emulsion; or drug suspension is atomized into a cryogenic liquid such as liquid nitrogen to produce frozen nanoparticle which are subsequently lyophilized to obtain free-flowing powder [44-48]. The rapid freezing rate caused by the low temperature of liquid nitrogen and the high degree of atomization resulting from the impingement occurring between drug solution and cryogenic liquid leads to the formation of amorphous nanoparticle. Apart from liquid nitrogen, the drug solution also can be atomized into compressed fluid carbon dioxide, helium, propane, or other cryogenic liquids such as argon

or hydrofluoroethers. Highly potent Danazol nanoparticle contained in larger structured aggregates were produced by the SFL process [49]. The SFL powders exhibited significantly enhanced dissolution rates. The micronized bulk Danazol exhibited a slow dissolution rate; only 30% of the Danazol was dissolved in 2 min. Nonetheless, 95% of the Danazol was dissolved in only 2 min for the SFL highly potent powders. In a study, SFL Danazol/PVP K-15 powders with high surface areas and high glass transition temperatures remained amorphous and exhibited rapid dissolution rates after 6 months in storage [50]. When Danazol was formulated with PVA (MW22,000), PVPK-15, and polaxomer407 to produce micronized SFL powders that were freeze dried under vacuum or dried by ATMFD, rapid dissolution occurred when the SFL powders were introduced in to the dissolution media (51).

COMMERCIALIZED NANOTECHNOLOGIES

Various nanotechnologies already have been commercialized to help deliver poorly water-soluble drugs into the body. These technologies include the following:

Nanocrystal technology

A nanocrystal technology is a crystalline material with dimensions measured in nanometer, a nanoparticle with a structure mostly crystalline. The nanocrystalization is defined as a way of diminishing drug particles to the size range of 1-1000 nm. Nanocrystalization is thought to be a universal method that can be applied to any drug [52]. A further characteristic' is that drug nanocrystals are composed of 100% drug there is no carrier material as in polymeric nano-particles. Dispersion of the drug nanocrystal in liquid media leads to so called "nanosuspension" [1]. Nanocrystal technology (Elan Corporation, Dublin, Ireland) can be used to formulate and improve compound activity and final product characteristics of poorly water-soluble compounds. The nanocrystal technology can be incorporated into all parenteral and oral dosage forms, including solid, liquid, fast-melt, pulsed-release, and controlled-release dosage forms.

Nanocrystal particles are produced by milling the drug substance using a proprietary wet-milling technique [53, 54]. The Nanocrystal drug particles are stabilized against agglomeration by surface adsorption of selected generally regarded as safe (GRAS) stabilizers. The result is an aqueous dispersion of the drug substance that behaves like a solution—a nanocrystal colloidal dispersion that can be processed into finished dosage forms for all routes of administration. All nanocrystals in the two products were produced using the pearl mill technology by Elan nanosystems.

Rapamune was the first marketed product introduced in 2000 by Wyeth Pharmaceuticals (Madison, NJ). It is available in two formulations, as oral suspensions and as a tablet. (Sirolimus, Wyeth, Madison, NJ).It is immunosuppressant tablet developed with nanocrystal technology and is designed to give patients more convenient administration and storage than the oral solution. Nanocrystal technology is an enabling technology for evaluating new chemical entities that exhibit poor water solubility.

Emend It was the second product on the market introduced in 2001 by Merck (Winhouse station N.J).the drug is aprepitant used for the treatment of emesis .the drug nanocrystal are contained within a hard gelatin capsule as pellets. Aprepitant was formulated by this in order to make the drug easy to handle by healthcare providers &patients as capsules .But the pellets can be administered via a stomach tube .current studies are being undertaken to evaluate the change in pharmacokinetics between the pellets and capsules [1].

One needs to bear in mind that a higher loading of tablet with more than 125 mg drug in a 400mg tablet is near the critical amount which is about 30%. If the total drug content exceeds 30%, the possibility of drugs nanocrystals touch each other and fusing to larger crystal is enhanced. So, these are the special methods and technologies required to produce high nanocrystal loaded tablets .By applying this, up to 90% nanocrystal powder would be loaded in to tablets. This product once again explained or demonstrated the importance of an increased bioavailability nanonization [55].

Nanomorph Technology

Nanomorph technology (Soliqs Abbott GmbH & Co. Kg, Ludwigshafen, Germany) has developed that converts drug substances with low water solubility from a coarse crystalline state into amorphous nanoparticle. Nanomorph technology is based on a dissolution–precipitation concept that operates using water-miscible solvents for dissolution, followed by precipitation by aqueous polymer solutions. In this technology, the drug suspension in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately, the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous polymer solution induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Water redispersable dry powders can be obtained from the nanosized dispersion by conventional methods (*e.g.,* spray drying).By using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticle [56].

Nanoedge Technology

Nanoedge technology (Baxter Healthcare Corporation, Deerfield, IL) described the formulation method for poorly water-soluble drugs. It is a useful technology for active ingredients that have high melting points and high octanol-water partition coefficients, logP. It is based on direct homogenization, microprecipitation, and lipid emulsions. In microprecipitation, the drug first is dissolved in a water-miscible solvent to form a solution. Then, the solution is mixed with a second solvent to form a presuspension and energy is added to the presuspension to form particles having an average effective particle size of 400 nm to 2 µ [57]. The energy-addition step involves adding energy through sonication, homogenization, countercurrent flow homogenization, microfluidization, or other methods of providing impact, shear, or cavitation forces. A drug suspension resulting from these processes may be administered directly as an injectable solution, provided water-for-injection is used in the

formulation and an appropriate means for solution sterilization is applied. Nanoedge technology facilitates small particle sizes (<1000 nm [volume weighted mean]), high drug loading (10–200 mg/mL), long-term stability (up to 2 years at room temperature or temperatures as low as 5 °C), the elimination of co solvents, reduced levels of surfactants, and the use of safe, well-tolerated surfactants.

Nanopure Technology

In Nanopure technology (PharmaSol GmbH, Germany), poorly water-soluble drugs are transferred to drug nanocrystals *via* a high-pressure homogenization process. The drug powder is dispersed in a surfactant solution and the forces in the high-pressure homogenizer are strong enough to disintegrate the coarse drug powder into drug nanoparticle with a mean diameter, typically between 200–600 nm.

The drug powder is dispersed in a nonaqueous medium (*e.g.,* PEG 600, Miglyol 812) or a water-reduced mixture (*e.g.,* water-ethanol) and the obtained presuspension is homogenized in a piston-gap homogenizer. A suitable machine for the laboratory scale is the Micron Lab 40 (APV Deutschland GmbH). Nonaqueous dispersion media such as PEG or oils yield suspensions that are suitable for the direct filling of capsules and thus an intermediate step required when using pure aqueous nanosuspension is avoided. With nanopure technology, homogenization can be performed in a nonaqueous phase or phases with reduced water content. And, in contrast to more pronounced cavitation at higher temperatures, homogenization was similar or more efficient at lower temperatures, even below the freezing point of water [58].

Crititech technology

Crititech Technology (CritiTech, Inc., Lawrence, KS) is based on PCA. Crititech uses ultrasonic energy produced by a converging–diverging nozzle or an electromechanical oscillator to shatter droplets into even droplets. This technique alone would not cause submicron particles to form because the droplets tend to coalesce immediately into larger drops. In the crititech procedure, the drug-laden solvent is sprayed into a flowing stream of supercritical carbon dioxide, which allows for a rapid mass transfer of solvent into the stream of supercritical carbon dioxide. This rapid mass transfer forces precipitation or crystallization to occur before the coalescence of droplets. The ultrasonic nozzle-based process is capable of producing discrete nanoparticle in a narrow size range. Moreover, crititech's proprietary particle-harvesting device allows continuous processing of compounds in closed systems with complete recovery of solvents and carbon dioxide for reuse or safe disposal [59].

Nanocochleate Technology

Nanocochleate delivery vehicles (also known as bioral technology) are a broad-based enabling technology for the delivery many therapeutic products. These molecules are stable phospholipid-cation precipitates composed of simple, naturally occurring materials such as phosphatidylserine and calcium. They consist of alternating layers of phospholipids and

multivalent cations existing as stacked sheets, or continuous, solid, lipid bilayer sheets rolled up in a spiral configuration, with little or no internal aqueous space. Unique properties of nanocochleates have been used to mediate and enhance the oral bioavailability of a broad spectrum of important but difficult-to-formulate biopharmaceuticals, including compounds with poor water solubility, protein and peptide drugs, and large hydrophilic molecules. Nanocochleate formulations are widely suitable to a broad range of therapeutic applications which include the oral delivery of amphotericin B (bioral amphotericin B) a potential antifungal agent, orally and parentally having a good safety profile with reduced cost of treatment; [60] large DNA constructs and plasmids (bioral DNA vaccines and bioral gene therapy); peptide formulations; anti-inflammatory formulations (bioral aspirin); and peptide-based vaccines.

Biorise® Technology

Eurands biorise technology optimizes the delivery of drugs that are poorly absorbed due to their inherent solubility problems. By optimizing the thearepeutic performance of these types of drugs with biorise, Eurands offers numerous oppurtunities to its parteners to improve their product portfolio, rescue new chemical entities and provide better medicines to their customer.

Eurand's Biorise technology exploits the much faster dissolution rate of nanocrystalline and amorphous forms of drugs when compared to unmodified or even micronized forms. Biorise creates new physical entities (NPEs) by physically breaking down a drug's crystal lattice, resulting in drug nanocrystals or amorphous drug with enhanced solubilization properties, faster absorption and ultimately, increased absolute bioavailability. These NPEs are then stabilized in an inert biological carrier, generally a polymer, to prevent the processed drug from agglomerating or reverting back to its crystalline form.

Eurand has two alternative activation systems available that are used to convert a drug into its thermodynamically activated state. These systems provide flexibility and allow the technology to be applied to a range of compounds with differing characteristics:

High Energy Mechanochemical Activation (HEMA) involves the application of friction and impact energy to the drug, thereby increasing its entropy and transforming the drug into its activated state. This is a dry system, which maintains the drug/carrier matrix in a powder form at all times.

Solvent Induced Activation (SIA) is particularly suitable for thermolabile compounds and compounds with a low melting point. With this system, a drug can be solubilized in an appropriate solvent and layered on to swellable, crosslinked carriers. Controlled evaporation of the solvent and drying of the material creates nanoparticle and amorphous drug that are stabilized in a carrier. Compared to other solubility enhancing technologies, Eurands' Biorise system offers faster and more efficient processing times, is cost effective, and produces a stable product without the use of surfactants. The finished product is a drug powder, which can be incorporate into a variety of dosage forms including tablets and capsules [5].

Diffucap's ® technology

Eurand's Diffucaps technology is a flexible multiparticulate system that provides optimal release profiles for single drugs and drug combinations to reliably overcome the problems associated with pH-dependent insolubility encountered in the GI tract. This proprietary technology has been developed specifically for weak, basic drugs and involves the incorporation of pharmaceutically acceptable organic acid or a crystallization-inhibiting polymer onto inert cores and coating the drug-layered beads with proprietary functional polymers. Formulations using an acid core ensure an acidic environment surrounds the drug at all times, thereby producing a soluble drug in an *in vivo* environment where it would otherwise be insoluble.

Further, Diffucaps incorporates release-controlling polymers, a functional drug layer, core granules or crystals, and a protective coating in one technology, providing sophisticated control of drug delivery timing that goes beyond what a single technology system can provide. Drug beads are typically created by layering active drug onto a neutral core (such as sugar spheres or cellulose spheres) and applying one or more rate-controlling, functional membranes. The drug layering process can be conducted either from aqueous or organic solvent-based drug solutions/suspensions and results in a small (approximately 1.5 mm or less in diameter), spherical, and multilayered bead particle. The beads may then be filled into capsules or compressed into orally disintegrating tablets to create the final dosage form. The inherent flexibility of the Diffucaps system permits the easy adjustment of both dosage strength and pharmacokinetic profile to achieve the required *in vivo* results. Beads can have different release profiles, different active ingredients, or both – all in one product. For drug development partners involved in clinical testing, this simplifies dose ranging studies since the beads can be encapsulated separately to create separate study arms. For commercialization purposes, multiple strengths of a drug product can be created by using different quantities of the coated beads. The customized Diffucaps drug release system can also be used in combination with Eurand's other technologies to enhance drug solubility in the GI tract [5].

Do-Coop Technology

Do-Coop Technologies Ltd. Described Neowater ™, a water-based nanotechnology whose physical properties mimic that of intracellular water by introducing inorganic, insoluble crystals into water in a patented process. The presence of durable water-coated nanoparticle induces long-range correlations in the liquid water and leads to several important benefits for drug delivery at the molecular level. Each nanoparticle within Neowater, with its huge surface, creates an effect known as the "surface effect," and in turn organizes the water molecules surrounding it. This stable system of largely hydrated nanoparticle, like non-ionic detergent derived micelles, reduces the entropy of aqueous solutions. In addition, by design, Neowater exhibits both hydrophilic and hydrophobic properties. When used in conjunction with therapeutics, Neowater allows for enhanced effective cell membrane permeability, enhanced drug efficacy, improved drug solubility and bioavailability, as well as improved enzyme activity, and stability under different stress conditions. An innovative patented Nanotechnology system

has been developed by a Drug Development Company located in Israel. This technology has brought the drug development process into a completely new level [61].

Biodis technology

Physica Pharma has developed Biodis®, a technology that enables to overcome solubilisation limitations to provide efficient drug absorption. Biodis® technology is based on the application of reactive lipid based carriers enabling to form a thin dispersed system in gastro-intestinal fluids. This system maintains the drug in a dissolved state in the physiological milieu and therefore facilitates its absorption through epithelium cells [62].

CONCLUSION

The growing percentage of NCEs displaying solubility issues demands that technologies for enhancing drug solubility be developed to reduce the percentage of poorly soluble drug candidates eliminated from development as a result. Drug cyclodextrin inclusion complexes, surfactant addition and particle size reduction via comminution, spray drying and solvent recrystallisation, possess significant limitations on the extent to which they may solubilise insoluble and nearly insoluble compounds. Novel technologies, such as sonocrystallisation, supercritical fluid processing, nanotechnologies such as nanosuspension, nanoemulsion, spray freezing in to liquid and some commercialized technologies such as nanocrystal, nanomorph, naopure, nanoedge, crititech, nanocochleate, biorise®, diffucaps®, biodis etc. present novel methods of solubilisation that may allow for greater opportunities to deliver poorly soluble drugs.

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