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Nanopharmaceuticals: A Review on Patent Expiring Novel Drugs and its challenges to Generic Drug Development

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ABSTRACT

Engineered nanoparticles are employed in nanopharmaceuticals, an advanced class of medicine, to improve drug delivery, solubility, bioavailability, and targeting efficiency while minimizing harmful effects. After overcoming many obstacles such as economic downturns and market failures, very few nanopharmaceuticals are getting authorized effectively. The manufacturing of generic pharmaceuticals becomes more competitive as soon as the patents on these marketed medications expire. For the community of low-income individuals, these generic medications provide accessible substitutes for expensive pharmaceuticals. Manufacturers of generic drugs must overcome obstacles before being allowed to enter the market. This review addresses upon medications whose patents are about to expire as well as the difficulties in developing generic pharmaceuticals.

Keywords: Nanopharmaceuticals, patent expiration, drug delivery, Economic down turns, obstacles, nanomedicine, generic drug, developing generic pharmaceuticals, CDDS: Conventional Drug Delivery System.

INTRODUCTION

Nanopharmaceuticals are advanced form of medicines having vital role in drug delivery system. It uses the particles engineered at nanoscale of size 1-100nm, in which characteristic phenomenon sanctions novel applications. Nanopharmaceuticals are pharmaceutical drugs accommodating nanomaterials and are employed for diagnosis, therapies, healthcare provisions. Nanomedicine is focal area for many research. Nanomedicines have been patented and approved by USPTO & USFDA respectively in US. Doxil™ (Doxorubicin HCl, Janssen) first nanodrug approved by FDA for cancer therapy in HIV patients in 1995.[1-4] Patent is a monopoly , generally a legal document granted to an inventor for his invention by the government. It is an intellectual property that protects exclusive rights of patentee against competitors who create similar drugs and therapies over 20 years.[1,5,6] Gives the owners exclusive power over inventions and prevent others from economically benefiting from inventions without creator's permission during the term of patent. Securing patent and retaining market exclusivity can be a massive process, especially in pharmaceutical sector. Pharmaceutical companies at present facing higher cost for drug discovery and development. As research costs rocketing, aggressive competition from generic drug companies becoming greater. Generic drugs are medicines designed identical to existing approved brand name drugs. Generic drug

companies are awaiting to compete as soon as the patent expires and these generic drugs cost significantly decreases this results in substantial savings for consumers. Apart from the benefits there are research-based challenges like purity, potency, stability, and drug release unique to development of generic drugs.[5-8] Many nanodrugs are on their way to patent expiration. Analysing Patent expiring nano pharmaceuticals and the challenges involved in generic drug development may impact on ensuring generic product quality in the market.

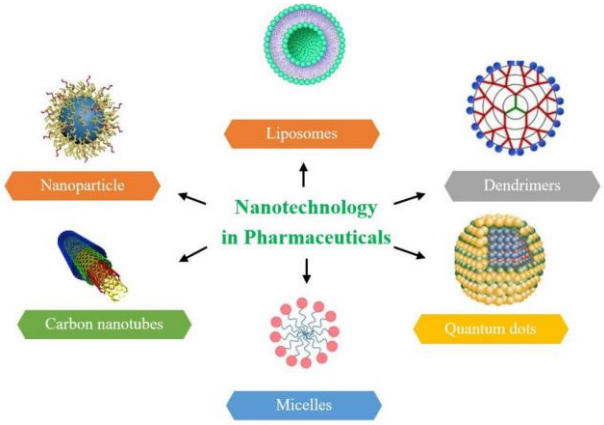

Figure 1: Nano pharmaceuticals. [9]

Nanopharmaceuticals

Nanopharmaceuticals is the combination of Nanotechnology and pharmaceutics. Nanotechnology specifies the use of technology at nanoscale (10^{-9}). One of the most exciting new technologies of 21st century is Nanotechnology. These changes in nanoscale at atomic or molecular level increased performance in various dosage forms. Nanotechnology is capacity to apply the theory of nanoscience to practical situations by seeing, quantifying, assembling, controlling and creating matter at nanoscale. *"A science, engineering and technology conducted at nanoscale, where unique phenomenon enable novel applications in a wide range of fields, from chemistry, physics and biology to medicine, engineering and electronics,"* is how the National Nanotechnology Initiative (NNI) in the US defines the nanotechnology.[9-10]These novel nano-based systems can act as clinical agents by themselves and notably act as a vector to carry the agents like active pharmaceutical ingredients/ probes/ proteins into specific region of the body either by attracting or absorbing them. Drugs entrapped in nanoparticles are intended to either improve drug delivery to or uptake by target cells, or lessen the toxicity of the free drug to organs that are not intended targets. Nanostructured materials overcome the imperfections of Traditional dosage forms.[11-12] Numerous biophysical techniques, including spectroscopy, scattering techniques, electron microscopy imaging, mammalian cell culture, and animal studies, are used to characterize the properties of nanomaterials, including morphology, structure, hydrophobicity, purity, drug release properties and toxicity. Nanomaterials have significant opportunities in pharmaceutical industries for drug delivery (oral, parenteral, ocular, pulmonary), gene delivery, gene therapy, tissue engineering and diagnosis.[13] Numerous nano pharmaceuticals like Liposomes, Niosomes, Carbon nanotubes, Nanocrystals, Quantum dots, Dendrimers, Polymeric nanoparticles, Metallic nano-particles, Polymeric micelles, Nanoconjugates and a lot more are commercially available.

Nanomedicine: The application of nanotechnology in biological sciences and

pharmaceutical field to bring therapeutic and healthcare benefits for patients in general is now referred to as "Nanomedicine" and it is rapidly expanding field of study. The US FDA has authorized commercialization of 100 nanomedicines applications and devices within last few decades. This demonstrates how important nanotechnology is to modern biomedical science. A vast array of materials and structures can be considered as nanocarriers. They can increase the safety and efficacy of active pharmaceutical ingredients (APIs) by accommodating a range of physiochemical features and modifying their biodistribution. Functional nanomaterials, for example, are primarily produced in the size range of 20–200 nm or even larger for use in biological applications. Nanostructures can be categorized as zero-dimensional objects (nanospheres, nanoclusters), one-dimensional objects (nanofibers, nanowires, nanotubes), two-dimensional objects (nanoplates, nanosheets), and three-dimensional objects (structures made of individual blocks in the nanometer scale, or bulk materials) based on the number of dimensions in the nanometric range.[2,12]

Drawbacks of CDDSs

One of the drawbacks of conventional DSSs is difficulty of eliminating the systems leftover components, which leaves non-biodegradable material in patients body and may be poisonous, is the major issue. Additionally, majority of traditional DDSs have a high first burst of drug release right after drug administration, and they also typically have limited drug solubility. Another major drawback of CDDSs is low drug stability, which occurs when the drug is easily broken down by the body's biological fluids and micro-environments.[2,14]

Patent Approval for Nano pharmaceuticals

Numerous medications have already received FDA and USPTO approval and patents. FDA has allowed the marketing of anticancer nano formulations that have been created and patented in the past, including Paclitaxel (AmbraxneTM), Daunorubicin (DaunoXomeTM), and Doxorubicin (Doxil™). Section 505(b)(j) of the Federal Food, Drug & Cosmetic Act prohibits nano formulations from applying for FDA approval through an Abbreviated New Drug Application (ANDA), as they are typically not bioequivalent to their parent version. Such medications must file a New Drug Application (NDA) with the FDA in accordance with section 505(b) (1). However, an ANDA can be submitted and approved as a New Chemical Entity (NCE) by the FDA if it is determined that nanoformulations are bioequivalent to their parent counterparts. The Patent Office's capacity to effectively control nanopharmaceutical products is limited by the absence of a defined system for nanomedicines. Although there are guidelines for lowering particle size, weight, and size ratio, they are not enough to oversee the whole nanopharmaceutical sector. To improve the PTO's structure and unique guidelines, reforms are required.[1]

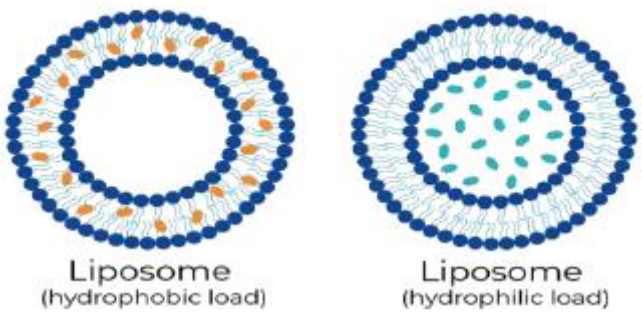

Figure 1: Schematic representation of Liposomes. [18]

Liposomes: Lipid-Based Nanodelivery System

The phrase "Liposome" is a combination of two Greek words: "Lipos," which means fat, and "Soma," which means body. It is related to the phospholipid molecules, which are the structural building blocks of the body. Stable substances can be entangled by lipidic vesicles, protecting their essential characteristics.[15-16]Diameter ranges from 0.01-0.5µm are colloidal transporters.[9]Liposomes, which are utilized extensively in the food, cosmetic, farming industries and pharmaceutical industries, are self-assembled, closed, spherical structures with a lipid bilayer made up of one or more amphiphilic phospholipids. Liposomal vehicles, whether made of natural or synthetic lipids, are hydrophilic and hydrophobic by nature and are biocompatible, biodegradable, non-toxic, and non-immunogenic carriers of active compounds. The scientific community has been aware of liposomes for more than fifty years. The British researcher Alec D. Bangham, who was researching the behaviour of phospholipids, introduced liposomes in 1961. The late 1990s saw the commercialization of liposomal formulations and significant advancements. First, liposomes were used by Gregoriadis et al. as drug delivery systems.[17]

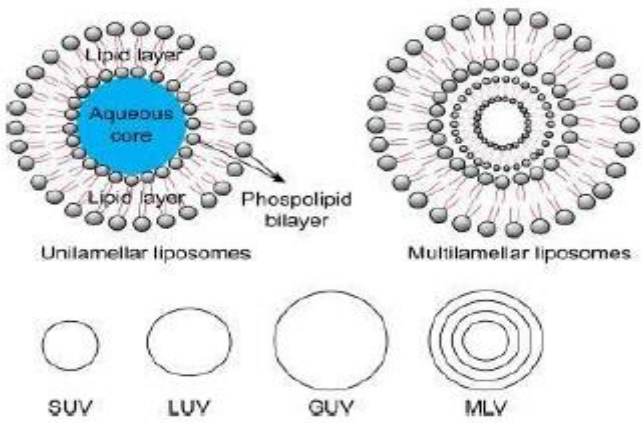

Figure 2: Diverse types of Liposomes. [19]

Categorization of liposomes:

Based on size and number of layers, liposomes can be roughly categorized as follows. Multilamellar vesicles (MLV) are made up of many lipid molecules separated from one another by an aqueous solution layer. These vesicles are greater than a few hundred nanometers in diameter. A single layer of lipids surrounds minute unilamellar vesicles (SUV), which have a diameter of 25–50 nm. One 100 nm-diameter lipid bilayer envelops large unilamellar vesicles (LUV). Liposomes are categorized as conventional liposomes (CL), pH-sensitive liposomes, cationic liposomes, long circulating liposomes (LCL), and immuno-liposomes based on the material from which they are generated.[9,15]

Liposomes-Mediated Drug Delivery System

Hydrophilic solutes that cannot pass through the lipids are liquefied by liposomes, which also liquefy hydrophobic solutes in the bilayer region and compress an area of aqueous solution inside a hydrophobic membrane. They are therefore particularly versatile as drug delivery systems since they can be utilized to trap both hydrophilic and lipophilic medicinal molecules. Usually liposomes entrap proteins, peptides, dyes, nucleic acids[DNA, siRNA], antioxidants, enzymes and cancer treatments.[15-16] Liposomes are also frequently made to transport biomolecules (like antigens and monoclonal antibodies) that are attached to their surfaces as ligands. The FDA initially approved liposomes as nanodrugs for use in

clinical trials, known as IND status. Many nano-formulations utilizing liposomal delivery have been approved/ are being studied since the approval of Doxil in 1995. Analgesics, antifungal and anticancer medications are among the numerous liposome-containing nanodrugs that have received approval. In addition to lowering toxicity and systemic effects, they can be used to lower drug clearance.[4,20]

Merits: Biocompatible, biodegradable, and non-immunogenic, liposomes are bio nanomaterials. Because liposomes are easily shaped and amenable to structural modifications, their characteristics can be changed for a variety of uses. Liposomes have the ability to act as a continuous depot and to protect the medication they have encapsulated from the outside world. High absorption and bioavailability in comparison to other oral supplement formulations. Non-invasive: reduces the danger of infection and eliminates the pain and suffering associated with injections. Economical since a lesser dose can be used to get the same result.

Demerits:
Currently high Production cost. Possibility of instability. Inadequate manufacturing due to subpar ingredients and high particle size. In the blood, they have a shorter half-life and can occasionally experience oxidation and hydrolysis reactions. Liposomes may resemble cell membranes, yet they are still foreign materials to the host. Liposomes are recognized by the mononuclear phagocytic system (MPS) following contact with plasma proteins. As a result, liposomes are released. Increased intracellular delivery. The main obstacle in employing liposomes for medication delivery is the reticuloendothelial system's capability to absorb injected liposomal vesicle.[15,21]

Patent expiring Liposomal drug
Mepact® (Non-Pegylated liposome):
Dosage form: Lyophilised powder.[22]

Dose: 2mg/m^2 body surface area. Adjuvant therapy after resection: Once weekly treatments for an extra 24 weeks, for a total of 48 infusions in 36 weeks, after twice weekly treatments spaced at least 3 days apart for 12 weeks.

Figure 3: Mepact (Mifamurtida).

Company: Takeda
Active ingredient: Muramyl tripeptide phophatidyl ethanolamine (LMTP-PE OR mifamurtide).
Approved date: Primary authorization *06/03/2009 EU,* launched by Takeda from Feb 2010 and latest renewal date: *20/02/2019*
Patent expiry: 2028[23]
Activity: Osteosarcoma
Storage conditions: Store in a refrigerator 2-8°C. Do not freeze. Keep vials safe from light within carton.
Shelf life: Powder vial not opened- 30 months, Reconstituted suspension: Up to 25°C, six hours of chemical and physical stability have been shown. It is advised to use right away from a microbiological perspective. Users are responsible for storing reconstituted products under proper circumstances and for no more than six hours at 25°C. If the solution is not used right away, it must be filtered and diluted before being used. Avoid freezing or storing the solution in a refrigerator.

Patent no: EU/1/08/502/001
MOA: Muramyl dipeptide (MDP), the smallest naturally occurring immunological

stimulatory component of Mycobacterium sp. cell walls, has a fully synthesized derivative called Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine, MTP-PE). Its immunostimulatory effects are comparable to those of natural MDP. MEPACT is a liposomal formulation that is intended to be infused intravenously and target macrophages in vivo. MTP-PE is a particular ligand for the NOD2 receptor, which is mostly present on macrophages, dendritic cells, and monocytes. MTP-PE is a strong monocyte and macrophage activator. Mifamurtide-induced human macrophage activation is linked to the synthesis of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1), as well as cytokines such as tumour necrosis factor (TNF-), interleukin-1 (IL-1), IL-6, IL-8, and IL-12. Human monocytes treated in vitro were not harmful to normal cells, but they killed both autologous and allogeneic tumor cells, such as those from melanoma, ovarian, colon, and renal cancer. Mifamurtide administered in vivo inhibited the formation of tumors in models of lung metastasis, skin and liver cancer, and fibrosarcoma in mice and rats. Mifamurtide was used as adjuvant therapy in the treatment of canine osteosarcoma and hemangiosarcoma, and it was shown to significantly improve disease-free survival. It is currently unknown how precisely mifamurtide induced stimulation of macrophages and monocytes causes anti-tumor action in both people and animals.

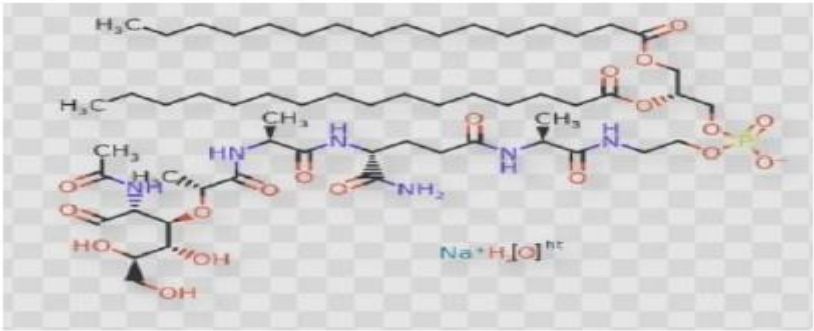

Figure 4: Mifamurtide chemical structure.[24]

Liposomes	API	Approved year/area	Dosage form	Route of administration	Indications
Other applications					
AmBisome	Amphotericin B (ampB)	1997, US	Lyophilisation	IV	Systemic fungal infection
Arikayce	Amikacin sulfate	2018, US 2020, EU	Suspension	Oral inhalation	Lung diseases
Vaccines					
Mosquirix™	Proteins on the surface of Plasmodium falciparum	2015, EU	Suspension	IM	COVID-19
Comirnaty™	mRNA	2021, US & EU	Suspension	IM	Malaria

Table 1: Table of other patented Liposomes.

Side effects: Most patients, especially those receiving Mifamurtide for the first time, experience chills, fever, and fatigue; these side effects are usually mild to moderate and temporary, and can be managed by your doctor with, for example, paracetamol for fever. Treatment with Mifamurtide can often result in stomach issues, such as

nausea, vomiting, and loss of appetite when used in addition to chemotherapy. Very common side effects (which can affect more than 1 in 10 people) includes: Cold, low body temperature, low RBC, sweating, pain, coughing, weakness, nausea, vomiting, headaches, fluctuations in heart rate, lack of appetite, discomfort.

Warnings: If you have asthma, inflammatory or autoimmune disorders, stomach issues, allergic responses to medications, heart or blood vessel problems, or feel warm, speak with your doctor before using Mifamurtide. Treatment with mifamurtide may need to be postponed or stopped if symptoms worsen or continue. A fever with a low white blood cell count may be a sign of a dangerous illness, so speak with your doctor if you have ever had asthma, corticosteroids, autoimmune or inflammatory diseases, allergic responses, stomach issues.

Niosome-Based Delivery System

The concept of targeted drug delivery is designed for attempting to concentrate drug in the tissues of interest while reducing the relative concentration of medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.

Among these carriers, niosomes are best. Researchers working in the cosmetics business initially reported on the self-assembly of non-ionic surfactants into vesicles in the 1970s. Niosomes, also known as non-ionic surfactant vesicles and are microscopic lamellar structures that are created when cholesterol and non-ionic surfactant belonging to the alkyl or dialkyl polyglycerol ether classes are combined.[(26)] They might function as a depot, releasing the medication in a regulated fashion. Delaying the medication's clearance from the bloodstream, shielding it from the biological environment, and limiting its effects to the targeted cells can overall enhance the therapeutic efficacy of the drug molecules. Bola-surfactant containing noisome is defined as alpha-omega-hexadecyl-bis-(1-aza-18crown-6), Span 80 and cholesterol (2:3:1 molar ratio).[(27)] Niosomes have been employed in research on the immunological response that antigens elicit. Haemoglobin can be transported by niosomes. Although niosomal drug delivery technology is still in its infancy, anti-leishmanial therapy and chemotherapy for cancer have demonstrated potential benefits from this kind of drug delivery system.[(28-29)]

Figure 6: Illustration of structure of Niosome[(25)]

Niosome composition

When it comes to niosome formulation, pharmacokinetic behaviour and application in cancer therapy, the makeup of the niosomes plays a critical role. The primary constituents of niosomes are typically

charge-inducing compounds, cholesterol and non-ionic surfactants; these substances are typically non-toxic and biocompatible. Because non-ionic surfactants have an amphiphilic structure with a polar head and a non-polar tail, they are the main constituents in niosome formulations. Since they require no specific handling or storage conditions and have superior stability, biocompatibility, and low toxicity, non-ionic surfactants are chosen over other surfactant molecules (positive, negative, and amphoteric).Literature sources state that the hydrophilic–lipophilic balance (HLB) value and the critical packing parameters are the primary attributes of non-ionic surfactants that affect niosome production. Dicetyl phosphate, phosphatidic acid, and stearyl amine are the most often utilized charged molecules in niosome formulation.[30-32]

A hydration medium is also necessary for niosome formulation, and phosphate buffer is widely used since it can help with both niosome formulation and the loading of natural or pharmaceutical compounds. The medium's composition and hydration conditions such as pH, temperature and time, have an impact on the drug or natural molecule release profile, size, distribution and entrapment efficiency. Niosomes are made up of a number of other chemical components in addition to these primary ingredients.

Patent Expiring Niosomal drug

Nintedanib [NTB]:

Brand name: Ofev / Vargatef

Other name: BIBF 1120

ATC Code: L01EX09

Nintedanib is used to treat idiopathic pulmonary fibrosis and, in combination with other drugs, certain forms of non-small-cell lung cancer. It is a member of the tyrosine kinase inhibitor medication class approved in 2014 and 2019 by the United States Food and Drug Administration. When used orally, it has a limited bioavailability (4.7%) because of first-pass metabolism. For improved bioavailability, a high dose of the medication 100– 150mg causes hepatotoxicity and gastrointestinal distress. Its bioavailability improves when administered via other routes, such as the lymphatic or transdermal systems. It is applied as the main therapy for fibrosis of the lung. It doesn't treat illnesses; instead, it inhibits the advancement of lung fibrosis.

Figure 7: Ofev (Nintedanib)

Dosage form: Oral dosage form (capsules)
Dose: 150mg/day (2 Times)
Company: Boehringer Ingelheim
Active ingredient: Triglycerides, Hard fat, Lecithin, Nintedanib
Approved date: October 15, 2014
Patent expiry: June 4, 2029
Activity: Pulmonary Fibrosis
Elimination half life: 10-15hrs
Patent Details: Pat.no CN104844499A *2015-06-05- 2015-08-19 Title Synthetic method for preparing Nintedanib through one-pot process.

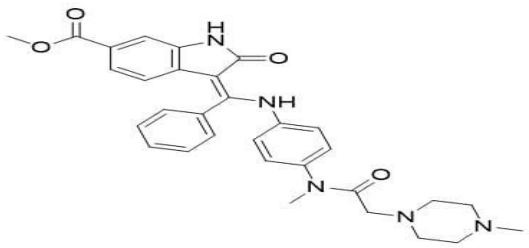

Figure 8 : Chemical structure of Nintedanib.[33]

MOA: Nintedanib is a multi-targeted tyrosine kinase inhibitors that work by inhibiting pathways involved in the pathogenesis of ILDs1-3 Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal disease characterised by fibrosis of the lung parenchyma and loss of lung function. Although the pathogenic pathways involved in IPF have not been fully elucidated, IPF is believed to be caused by repetitive alveolar epithelial cell injury and dysregulated repair, in which there is uncontrolled proliferation of lung fibroblasts and differentiation of fibroblasts into myofibroblasts, which excessively deposit extracellular matrix (ECM) proteins in the interstitial space. A number of profibrotic mediators including platelet-derived growth factor (PDGF),[34] fibroblast growth factor (FGF) and transforming growth factor-β are believed to play important roles in the pathogenesis of IPF. Nintedanib is a potent small molecule, inhibitor of the receptor tyrosine kinases PDGF receptor, FGF receptor and vascular endothelial growth factor receptor.

Side effects: Diarrhea, Nausea, Vomiting, Heart attack, Chest pain, Bleeding problems, Headache, Weight loss, High blood pressure.

Warnings: Do not take more than 300mg in 1 day, Hepato-toxicity, Gastrointestinal perforation, proteinuria.

Table 2: Table of other patented Niosomes.

Niosomes	API	Approved year	Dosage form	Route of Administration	Indication
NSAIDs					
Voltaren	Diclofenac Sodium	2014	Gel	Topical	Osteoarthritis pain
Antimicrobial					
Erythromycin Niosome Topical Solution	Erythromycin	2013	Solution (2%)	Topical	Skin infections like Acne, Dermatitis
Periochip	Minocycline	2006	Dental implants	Intra-pocket/ Subgingival/ Topical	Periodontis

The Science of Nanocrystals

Nanocrystals are pure solid drug particles within 1000nm range. These are 100% drug without any carriers molecule attached to it and are usually stabilized by using a polymeric stearic stabilizers or surfactants. A nanocrystals suspension in a marginal liquid medium is normally alleviated by addition of a surfactant agent known as nano-suspension. In this case, the dispersing medium are mostly water or any aqueous or non-aqueous media including liquid polyethylene glycol and oils. Nanocrystals possesses specific characters that permit them to overcome difficulties like increase saturation solubility, increased dissolution velocity and increased glueyness to surface/cell membranes. The process by which nanocrystals are synthesized are divided into top-down and bottom-up approaches. The top-down approach includes, sono-crystallization, precipitation,

high gravity controlled precipitation technology, multi-inlet vortex mixing techniques and limited impinging liquid jet precipitation technique. However, use of an organic solvent and its removal at the end makes this process quite expensive. The bottom-up approach involves, grinding procedures along with homogenization at higher pressure. Among all of the methods, milling, high pressure homogenization, and precipitation are the most used methods for the production of nanocrystals. The mechanisms by which nanocrystals support the absorption of a drug to the system includes, enhancement of solubility, suspension rate and capacity to hold intestinal wall firmly. Niet embedded cinaciguat nanocrystals in chitosan microparticles for pulmonary drug delivery of the hydrophobic drug. The nanoparticles were contrived for continuous release of the drug taking advantage of the swelling and muco-adhesive potential of the polymer. They found that inhalation efficacy might be conceded under the disease conditions, so more studies are needed to prove that this system has more potential.[35-36]

Figure 9: Framework of Nanocrystals.[37]

Nanocrystals Characterization

Nanocrystals (NC) are a type of pharmaceutical products that use the concept of nanoscience combined with the crystalline properties of drugs to achieve better results in solubility, dissolution, physical and chemical properties. Compared with other bulk materials, NC often faces many physical and chemical stability problems during production and storage. Therefore, various control methods to apply them in drug delivery are important steps in the development of NCs. There are many ways to ensure the uniformity of state in NCs and their clinical results. [38]

Drug nanocrystals in the commercial pharmaceutical development process:

Nanosize is one of the most important drug delivery platforms in the commercial development of poorly soluble molecules. From a commercial perspective, the two most important processes used on a commercial scale are wet ball milling and high-pressure homogenization. Initial problems such as abrasion,long milling time, and other difficulties during operation have been resolved. As the biopharmaceutical aspects of poorly soluble drugs are better understood, the in vivo success of drug nanocrystals is also becoming clearer. Alternative methods such as bottom-up methods or combined methods have gained considerable interest. Nanosuspensions are now used in all phases of commercial drug development because nanotechnology ranges from the milligram scale to the production scale. Formulation method decisions are important.[39-41]

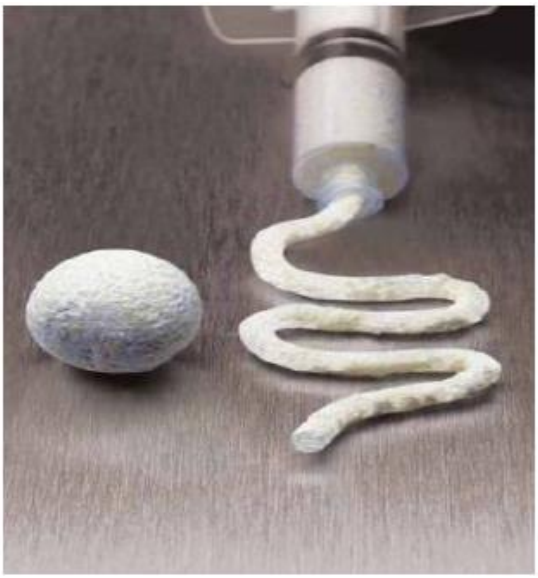

Figure 10: EquivaBone (Bone Graft Substitute). [49]

Nanocrystals for Delivery of Therapeutic Agents:

The medical use of many chemical compounds seems to be a difficult task due to their poor water solubility and bioavailability problems. The process of the nanoscale state of NCs can accelerate absorption, increase saturation solubility, and improve bioavailability. Nanocrystals are crystalline particle clusters with dimensions less than 1000 nm. Special surface properties, high loading capacity, improved bioavailability, low hunger/nutrition status changes, low incidence of side effects can be achieved by various routes such as enteral, parenteral, lung, dermis, etc., active and various passive targeting. Current technologies for commercial applications provide a potential platform for drug delivery research using nanocrystals. It is estimated that nanocrystals will account for 60% of all nanotechnology products in 2021 and the market size will reach $82 billion. The recent increase in the production and commercialization of whole nanoparticle systems highlights the need for further development of nanocrystals. Exploring the potential of synchronized target delivery could aid in the treatment of infectious diseases, disease-related illnesses, and even cancer.[42-44]

Patent Expiring Nanocrystal Drug

EQUIVABONE® Bone graft substitute [45]

Dosage form: Paste/injection

Drug: Nanocrystalline Hydroxyapatite

Dose: But an average posterior dose is 2.5mg/level. Average interbody dose is 5mg/level.

Company: ETEX Corporation

Active ingredients: Calcium phosphate, hydroxyapatite, bioactive glasses. [46]

Other ingredients are: Synthetic polymers (poly-glycolic acid & poly-lactic acid), natural polymers (collagen based matrices & fibrin) and polysaccharides (hyaluronic acid &

Approved date: February 5, 2009 by FDA.

Activity: Equiva Bone Bone Graft Substitute combines the osteo inductivity of demineralized bone matrix (DBM) with the osteo conductivity, moldability, migration resistance, and hard setting characteristics of proprietary nanocrystalline* calcium phosphate technology.[47] Osteo induction is a process which induces osteogenesis. Osteo induction is the process of drawing in immature cells and encouraging them to differentiate into preosteoblasts. Osteoinduction is primarily responsible for the majority of bone healing in situations involving fractures. Bone grows osteoconducting, meaning it does so on a surface. It is common to observe this phenomena in relation to bone implants.[48]

Patent details: On Jun. 7, 1999, and entitled "Bone Graft Substitute Composition", the contents of which are incorporated by reference in their entirety.
US Patent (7,514,024): Title: Nanocrystalline hydroxyapatite based compositions and methods
Assignee: Nycomed Danmark ApS (now part of Pfizer)
Filing Date: March 24, 2005
Grant Date: March 31, 2009
Expiration Date: Estimated March 24, 2025 (prone to changes in the patent term)
MOA: Equiva Bone is a biocompatible bone substitute Articles containing synthetic calcium phosphate, Carboxy methylcellulose (CMC) and human demineralization bone matrix (DBM). Available in single-use products. Mixed sterile powder and hydrated solution build together when used in the office. Flowable paste, can be implanted manually extruded from a syringe. Premium dental implant products hardens, absorbs and reshapes body heat Article Immediate correction. All DBM categories available EquivaBone for osteoinductive potential determination.[50]
Side Effects: Allergic reaction, Gastrointestinal issues (diarrhoea, colic), Changes in behaviour (eg: restlessness).
Warning: Equvabone is used in veterinary medicine as a bone graft substitute to promote bone healing. Some warnings and precautions regarding its use are:
Hypersensitivity reactions: Monitor for signs of hypersensitivity or anaphylaxis after administration.
Risk of infection: As with any surgery, there is a risk of infection
Contraindications: Use with caution in animals known to be sensitive to any part of the transplant.

Table 3: Table of other patented Nanocrystals.

Nano crystals	API	Approved year	Dosage form	Routeof administration	Indication
Tricor	Fenofibrate	2004	Tablet	Oral	Hyperlipidemia
Zanaflex	Tizanidine HCL	2002	Tablet/Capsule	Oral	Muscle relaxant
Venofer	Iron sucrose	2000	Injection	Intravenous	Iron deficiency in chronic kidney disease (CKD)

Generic Drugs: A Cost Effective Alternative

A generic medicine is a pharmaceutical that is made to have all the same qualities, performance characteristics, safety, dosage form, strength and mode of administration as an officially recognised brand-name product.[7]
Once the patent on the original medication manufacturer's product expires, generic drugs which are less expensive equivalents of branded drugs are introduced to the market. Chronic diseases and sedentary lifestyles drive generic drug market growth. The short time between new medication expiration and re-filing stimulates companies to
create generic drugs, which further lowers the prices of generic drugs due to increased competition. Government agencies take a number of steps to raise awareness of the availability of generics, such as the "*Pradhan Mantri Bhartiya Janaushadhi Pariyojana (PMBJP)"*, which aims to provide high-quality generic medications and implants at reasonable costs through *PMBJP Kendras* nationwide. Additionally, the Covid-19 pandemic has significantly increased the export of generic medications as both the developed and developing worlds are searching for less expensive alternatives to copyrighted medications because to their high cost.[51]

Historical Overview of Generic Drugs:

In the United States, the generic medication industry has been controversial since the pharmacy and medical communities were founded in 1888. The *Federal Food and Drugs Act* of 1906 was enacted to curb

adulteration and misbranding. Concerns about generic medications replacing name-brand ones first surfaced in 1928. Congress approved the *Federal Food, Drug, and Cosmetic Act* (FDCA) in 1938, making items released after that year new medications and requiring FDA approval and manufacturer testing to prove their safety.

Two different types of medications were created by *the Durham Humphrey Amendment of 1951:* those that require a prescription and are dangerous to use without medical supervision, and those that are available for sale without one. These restrictions restricted the production of generic goods of adequate quality but assisted in preventing the substitution of inferior goods. *The Kefauver-Harris Drug Amendments of 1962* mandated that pharmaceutical companies demonstrate a product's safety and effectiveness to the FDA prior to putting it on the market. The FDA's approval of "literature-based" New Drug Applications created a new method for demonstrating safety and effectiveness. Additional laws passed in 1967 and the 1965 Medicaid and Medicare modifications to the Social Security Act contributed to the rise of generic drug goods. The FDA could authorize applications to commercialize generic versions of brand-name medications issued after 1962 without having to repeat efficacy and safety studies according to *the Hatch Waxman Act,* commonly known *as the Drug Price Competition* and *Patent Term Restoration Act.* The licensing procedure, bioequivalence concerns, and corruption are some of the difficulties that have surrounded generic medicine laws during the past 30 years.

Approval of Generic drugs:

The ANDA is used in the approval procedure for generic medications and does not require clinical data on safety and efficacy. For a generic medication to be approved for sale, it must be produced in compliance with FDA Good Manufacturing Practice guidelines, meet batch standards for identity, strength, purity, and quality, and be therapeutically equal to the branded product. Drugs must be pharmaceutically bioequivalent in order for generics to be considered therapeutically equivalent. The AUC and the maximum drug concentration (C_{max}) are assessed to determine bioequivalence. If the relative mean C_{max} and the mean AUC have a 90% confidence interval CI between 80% and 125%, the generic product qualifies as bioequivalent. Yet, some medical professionals continue to express reservations over the interchangeability of generic drugs and narrow-therapeutic-index (NTI) branded medications. Although there is no testing to establish whether generic products are bioequivalent to one another, it is anticipated that there won't be any notable differences in their efficacy.[8]

CASE STUDY OF METFORMIN:

Metformin (sold under the name Glucophage etc.) is an important first-line medication for the treatment of type 2 diabetes especially for obese individuals. The risk of developing metabolic syndrome in patients taking antipsychotic medications. It has also been shown to reduce pain and is not associated with weight gain. It is taken orally. Metformin is generally well tolerated. Side effects include diarrhoea, nausea and abdominal pain. There is a small risk of causing hypoglycemia. If the drug is used in high doses or given to people with serious kidney problems, high levels of lactate in the blood (acidosis) may occur. Metformin is a biguanide antihyperglycemic drug. It works by lowering blood sugar levels, increasing insulin sensitivity of body tissues, and decreasing appetite and calorie intake by increasing the release of GDF15. Metformin was first described in the scientific literature in 1922 by Emil Werner and James Bell. French doctor Jean Sterne began studying the human body in 1950. He introduced the drug in France in 1957. It is available as a generic drug.[52-55]

The majority of patients with type 2 diabetes mellitus will eventually require

combination therapy involving two or more agents to achieve their glycemic target as their disease progresses. The American Diabetes Association and the European Association for the Study of Diabetes (ADA), as well as the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE), have launched a joint effort to recommend that treatment options for patients with type 2 diabetes should both aim to lower (A1C) levels and that treatment and combination therapy should be individualized for each patient. Combination therapy should also include drug classes that are effective and have a proven track record of success in terms of the pathophysiology of type 2 diabetes. However, the ADA and AACE recommend metformin as the first line oral treatment, but the ADA encourages the use of sulfonylureas[(56)] or insulin in patients who are not meeting their A1C goals, while the AACE recommends the newer incretin drugs, such as glucagon, which have been used much earlier and more frequently. The mechanisms of action, benefits, and risks of traditional and newer medications are discussed so that pharmacists can recommend the best combination of medications for people with pain.

A method of treating diabetes mellitus with an oral metformin hydrochloride tablet, comprising: administering the sustained-release tablet once daily to a human diabetic subject on a diet, wherein the sustained-release tablets contain Metformin hydrochloride and extended-release tablets, wherein the tablets do not utilize polymer swelling and the sustained-release tablets provide drug plasma concentration of metformin in human patients within 12 to 24 hours after administration; The sustained-release tablet exhibited the following in vitro dissolution profile when tested at 75rpm at 37°C in 900 ml of pH 7.5 phosphate buffer on a USP Type 2 apparatus: 0-25% metformin released after 2 hours; 10-45% metformin released after 4 hours; releases 30-90% of metformin after 8 hours; releases at least 50% of metformin after 12 hours; releases at least 60% of metformin after 16 hours, and 70% of metformin after 20 hours. Metformin is a medication that is only available with a prescription from your licensed medical provider.

Metformin is widely used in India and is often used as a first-line treatment for type 2 diabetes mellitus (T2DM). Manufacturing and marketing of the drug in India, Sun Pharma,

Cipla, Dr. Reddy's, Lupin, and Aurobindo.

Brands: Common brands of metformin in India include *Gluformin (Abbott), Glycomet (USV), Cetapin (Sanofi), and XMet (Lupin).* Metformin is available in a variety of forms and dosages, including extended-release (Metformin XR), combination drugs (such as metformin with a sulfonylurea, a DPP4 inhibitor, or an SGLT2 inhibitor).

Cheap and Affordable Price: Generic versions of metformin are available in India at low prices and suit the budget of the people. The price range is ₹5-15 per tablet depending on the brand, dosage and formulation (current version and delayed version).

Government Scheme: The "Jan Aushadhi Scheme of the Government of India" provides affordable medicines including metformin at discounted prices in rural and underserved areas.

Availability of metformin:

Urban areas: Metformin is readily available in public and private pharmacies, hospitals and medical stores in cities and semi-urban areas. Most clinics carry it because of its important role in controlling diabetes.

Rural areas: Availability of metformin may vary in rural areas, but most metformin is provided by government agencies such as National Health Missions (NHMs) and public clinics. It is also easily accessible from large pharmacies and medical centers.

Medicine and use: Metformin is prescribed by most doctors, endocrinologists, and

diabetologists for the treatment of T2DM. It is also combined with lifestyle changes such as diet and exercise.

Recommendation: *The Indian Council of Medical Research (ICMR)* and the *Indian Association of Physicians* recommend metformin as the first-line treatment for new patients with type 2 diabetes.

Challenges for the Generic Drug Development- A Metformin Comparison:

Majorly includes quality, economy and stability

1) QUALITY: As the medical sector develops, the number of drugs (brand and generic) on the market continues to increase, so controlling their quality is the most important issue for companies.[57] Quality drugs can be produced by the same or different pharmaceutical companies, sold under different names and at different prices, whether they are the same or different from the original drug.

In most cases, generic drugs and branded products have the same brand and active ingredient. Therefore, the generic drug must be the same or bioequivalent to the branded drug in terms of dosage form, safety, strength, method of administration, quality, well-characterized effect and readiness for use. Bad drugs that attract the attention of pharmaceutical companies have also found a place in the market.[58] This bad drug differs from the old drug in many ways such as Concentration, quality etc. Therefore, quality control should be carried out according to regulatory documents such as IP, USP, BP etc. during the production of the final product. Metformin (molecular formula $C_4H_{11}N_5$, molecular weight 129.167gm/mol) is the most common antidiabetic drug in the treatment of type II (non-insulin dependent diabetes). It is used to increase glucose absorption and increased peripheral glucose uptake and insulin sensitivity.[59] There are many types of metformin available in the market, so the quality of the different types of drugs available in the market should be checked well to help choose the right type of drug.

2) ECONOMY: The data on metformin allow us to compare the price changes of the "same" drug before and after administration for 500mg and non 500mg, and use the difference to record the different responses of the companies. The controlled and uncontrolled methods are comparable because both are oral tablets to be taken daily at home. No clinically significant response was observed at daily doses below 1500mg, suggesting that patients can meet their daily dosage needs with the established doses. Our quasi-experimental findings suggest that collusion occurred during the previous regulatory period to maintain the maximum price of 500mg metformin, in part by increasing the extended-release amount of the 500mg formulation, which was the higher average price. Of the 112 companies, 16 had at least a 1% market share in the 500mg formulation, 16 of which had the highest average price, and the company that set the highest average price. Metformin is the first-line oral hypoglycemic agent in international guidelines for the treatment of type 2 diabetes (T2DM) with proven efficacy, safety and cost-effectiveness. Metformin saves 39.87% to 40.97% in annual medical costs compared with other drugs. Price for patients weighing 60kg or more.

The increase of 60kg from 39.87% to 70.49% confirmed the results. The annual medical cost of Metformin is 1358.90¥ and finally metformin appears to provide better value for money.[60]

3) STABILITY: Metformin accumulation not only reflects the importance of pharmacokinetic differences with glycemic response but has also been shown to be an important factor in the death of lactic acidosis. Therefore, clinical drug monitoring (CDM) of metformin is necessary to confirm that metformin is within the recommended clinical range. Metformin stability studies become an important part of CDM bioanalysis by providing accurate drug information for appropriate treatment. The aim of this study was to investigate the stability of metformin hydrochloride in

plasma samples using HPLC equipped with a UV detector at 233nm wavelength. Combined separation was performed using isocratic elution technique. The mobile phase consisted of acetonitrile: phosphate buffer 6mM pH 5.2 (45:55) and a C18 column (4.6mm × 150mm, 5µ) at room temperature. The results showed that metformin hydrochloride products were stable at 25°C and 4°C for 6 hours and 30 days respectively. At the same time, metformin hydrochloride in plasma matrix was stable for 6 hours at 25°C and 1 day when stored at ≤20°C. This study recommends storing patients' plasma at 20°C for 24 hours during metformin CDM.[61]

CONCLUSION

Advanced pharmaceuticals known as nanopharmaceuticals are used to deliver drugs for treatment, diagnosis and other medical purposes. Patent coming outdated, Since there would be intense competition for producing generic drugs when the patent expires, makers of generic drugs can benefit from knowledge about nanopharmaceuticals. Due to their low cost and substantial saving for consumers, generic medications are in high demand on the market. Generic medicine development is aided by several federal and state initiatives that promote healthy competition. Generic medications are extensively utilized in India and PMBJP raised public awareness of this fact. However, given the possibility for bioequivalency difficulties, problems with quality and variability in individual patients, cautiousness is required. Branded medications provide proven results, creative formulas, exacting quality assurance, safety and efficacy. Patients and healthcare professionals should evaluate costs and benefits while taking the patient's requirements and circumstances are taken into consideration.

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