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Review Article

A Review On Novel Excipients

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ABSTRACT

The field of pharmaceutical formulation is constantly evolving, driven by the need for improved drug delivery systems and enhanced therapeutic outcomes. One critical aspect of this evolution is the development and utilization of novel excipients. This review explores the types and examples of novel excipients that have revolutionized drug formulation in recent years. Throughout this review, we delve into the applications, advantages, and limitations of these novel excipients, highlighting their pivotal role in shaping the future of pharmaceutical formulation. The utilization of these innovative materials not only improves drug efficacy and patient compliance but also offers exciting opportunities for personalized medicine and targeted drug delivery.

INTRODUCTION

In addition to the active pharmaceutical ingredient [API], many dosage forms created today are complex systems with numerous extra components. These substances are typically added to active pharmaceutical ingredients in order to:

1. Enhance the stability of the formulation: Excipients are incorporated to stabilize the active pharmaceutical ingredient [API], ensuring that the product remains stable over an extended period, thereby extending the shelf life of the dosage form. It is a common observation that pure API tends to lose stability quickly, leading to denaturation or adhering to container walls, making it unsuitable.
2. Adjust the formulation for precise dosing in potent medications: When dealing with potent drugs, additional substances are introduced into the formulation to facilitate the creation of an accurate and consistent dosage form.
3. Improve patient acceptability: Excipients can play a role in enhancing the acceptability of medications by improving their taste, texture, or other sensory attributes.
4. Enhance the bioavailability of active drugs: Excipients, for instance, can contribute to increasing the bioavailability of the active

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medicinal ingredient. Often, active ingredients like aspirin are poorly absorbed by the human body. In such cases, the active ingredient is either dissolved in or combined with an excipient, which can act as a solvent or aid in the absorption of the drug by the body.

5. Ensure the overall safety and effectiveness of the formulation during storage and usage.

Excipients are often referred to as these components, and the worldwide pharmaceutical excipient council defines excipient as **"Any substance other than active drug or pro-drug that is included in the manufacturing process or is contained in finished pharmaceutical dosage forms"**

The following are the excipient's ideal qualities:

- Possessing chemical stability,
- Demonstrating non-reactivity,
- Exhibiting low sensitivity to equipment and processes,
- Maintaining inertness within the human body,
- Showing non-toxic characteristics,
- Having acceptable sensory properties,

Proving efficient and cost-effective for the intended purpose. [1-5]

Types Of Excipients:

1. Base on origin: [6]

Types	Example
Animal	Lactose, Gelatine, Honey, Bees wax
Vegetable	Starch, Turmeric, Acacia, Guar gum
Mineral	Calcium phosphate, Silica, Talc, Paraffin
Synthetic	Boric acid, Lactic acid, Povidone

2. Base on their function: [7]

Type	Example
Lubricant	Talc, Stearic acid, Vegetable oil,
Diluent	Lactose, Sorbitol, Dextrose
Binder & Adhesive	Acacia, Gelatine, Glucose, Starch paste
Disintegrant	Starches, Cross link polymer, Cellulose
Solvent	Water, Alcohol, Acetone, Syrup
Buffer	Phosphate buffer, Acetate buffer
Preservative	Methyl paraben, Propyl paraben
Sweeteners	Mannitol, Saccharine

Novel Excipients:

A novel excipient is an excipient which is being used for the first time in a drug product, or by a new route of administration [ICH]. [8]

According to the FDA, a novel excipient is one that has never been used in a drug product that has received FDA approval and has not been proven to be effective in food. Outside of an investigational new drug [IND], new drug application [NDA], or biologics license application [BLA] that specifies a finished product to which the excipient has been added, FDA presently does not examine the safety of novel excipients.

Drug manufacturers have urged FDA to create new channels for the regulatory evaluation of innovative excipients as a result. Novel excipients, according to their proponents, may increase medication delivery or be useful in the creation of opioid formulations that inhibit abuse, among other potential benefits for public health. Additionally, the FDA's acceptance of a novel excipient would comfort pharmaceutical companies that they can employ them in drug development programs while lowering the possibility that the FDA would raise safety issues during the application review.

The FDA has unveiled a pilot assessment initiative aimed at evaluating the toxicological and quality aspects of new excipients designed for human medications. This initiative has been shaped, in part, by feedback from stakeholders. [9]

As per the criteria established by ICH, an excipient is classified as "novel" if it is being used in a human drug product for the first time. Notably, while the FDA maintains the IID [Inactive Ingredient Database], both U.S. and ICH standards do not differentiate between new chemical entities and minor alterations to approved excipients, co-processed blends of existing excipients, approved excipients proposed for new routes of

administration, or excipients approved for use in food or cosmetics. It's important to recognize that certain of these excipients may not require the comprehensive battery of tests outlined in the FDA's guidance for excipient safety evaluation. In such cases, excipient and pharmaceutical manufacturers must anticipate the requirements set forth by the regulatory agency during the drug application evaluation process. Any misjudgement in this regard could potentially lead to significant delays in the approval of drugs. [10]

Fig 1: Concept to launch.

When are excipients considered new or novel?

A chemical that is utilised for the first time in a drug product or for the first time in a novel mode of administration is referred to as a new or novel excipient under current EU rules. It could be a brand-new chemical compound or an old one that has never been utilised in a medicinal product inside or outside the EU. Additionally, pharmaceutical excipients that are utilised in a product for a specific drug administration pathway for the first time are regarded as novel. For instance, when a pharmaceutical excipient is used for the first time in eye drops after being used frequently in oral goods, it is regarded as new. Novel excipients promote innovation and, in the end, can enhance patient treatment options, but they must first establish their physicochemical features, performance, and safety. [11]

What are the challenges when novel excipients are introduced?

a) Regulatory framework

Novel excipients are not independently examined under the regulatory system in place right now. Only the initial application for a medication containing the new excipient is used to review them. As a novel compound, a new excipient has no specific regulatory approval procedure.[12]

Due to their novelty and the limited expertise with their safety and use in pharmaceutical products, new excipients are frequently difficult to employ. As a result, substantially more sophisticated and extensive information is needed to support their regulatory approval [marketing authorization] than it is for existing excipients. [13]

The law requires EU regulators to treat innovative excipients as new chemical entities. Every time a new excipient is used in a formulation, it must undergo a thorough toxicological examination, just like a new active substance [also known as an active pharmaceutical ingredient, or API] must. [14]

The reason why this group of ingredients is not suggested as the first choice in formulations for paediatric use is because of the lack of expertise with the use of novel excipients. Use of innovative excipients in paediatric formulations is cautioned by the EU guideline on pharmaceutical development of medications for paediatric use. [15]

The recommendation advises care even if it acknowledges that their usage is essential to pharmaceutical innovation and necessary and desired for paediatric formulations. Limited knowledge of their application in medicine formulations is the key cause for the caution. A novel excipient's additional value in a given paediatric pharmaceutical product must be carefully weighed against the usage of other excipients with known safety profiles, alternative dosage forms, or alternative routes of administration.

b) Scientific evidence

Complete manufacturing, characterisation, and control information should be included in the data package or scientific dossier that must be provided in support of a new excipient, together with cross references to relevant safety [non-clinical] data.

Data should be presented in a manner that is comparable to the format used for active substances, ideally as a standalone document. The non-clinical section of the dossier is expected to contain more details on toxicity tests using the novel excipient. The proper toxicological data must support the use of novel excipients.

Applicants are asked to suggest and justify the amount of toxicological testing used during the development of novel excipients because the definition of "appropriate" is frequently left undefined.

The requirements for toxicological testing for novel excipients may not be clearly defined, which could artificially raise regulatory expectations and cause discord. Different authorities may use their own definitions and specifications for "appropriate" toxicological data. Such ambiguity merely complicates the problem with novel excipients, which is already difficult. Acute toxicity studies, sub-chronic and chronic studies, genotoxicity studies, reproductive toxicity studies, and absorption, distribution, metabolism, and excretion [ADME] investigations should all be covered in toxicological data overall. Excipients used in pharmaceutical products are subject to risk-benefit assessment standards just like any new active ingredient.

Despite the fact that several unique excipients have been created for use in pharmaceuticals, they are not usually seen in pharmaceutical goods. Due to the stringent standards 5, it is believed that using novel excipients makes the regulatory review of new pharmaceutical products more difficult and increases the likelihood of approval process delays. Scientists working on formulations would wish to include excipients that perform optimally in the medication delivery system. To prevent unnecessary risks and delays in the approval process, they prefer excipients that are part of pharmacopeial monographs and have a pre-approved functional role in pharmaceutical products.

Priority	Substance type	Reason
1	Excipients that have previously been employed in similar drug products, administered through the same route, at equal or higher concentrations.	These excipients can be utilized without requiring further toxicological assessment or the submission of additional supporting information for regulatory approval of the drug product.
2	An exception is made for excipients that have been employed in a similar route of administration but at lower concentrations than those in the new product.	Only a minimal amount of supplementary preclinical evaluation is necessary.
3.	Excipients that have been utilized in drug products, albeit not for the exact same route of administration.	The excipients have a well-established safety record, and therefore, only a limited amount of additional pre-clinical data needs to be provided to demonstrate their safety when administered via a new route.
4.	An excipient previously employed in a cosmetic or food product that has been marketed.	There is access to certain safety data, reducing the requirement for extensive pre-clinical assessments. However, some pre-clinical evaluations are still necessary, albeit to a lesser extent compared to a new chemical entity.
5.	A novel excipient, meaning a new chemical entity that has not been previously employed in any drug, food, or cosmetic product-a freshly synthesized compound.	Comprehensive pre-clinical assessments must be carried out to establish its safety, and it is essential to ascertain the pharmacokinetics of the newly introduced excipient.

Table 1: Prioritizing pharmaceutical excipients is determined by their historical utilization in drug products, as well as their presence in food and cosmetic products.

The objective is to mitigate additional risks and prevent delays in the approval process for new drug products while also keeping development costs minimal.

Absence of harmonized and clear requirements

Complications may occur even when a well-established and previously approved compendial substance is administered through a new or alternative to an approved route of administration [for example, when a pharmacopeial excipient frequently used in oral dosage forms is used in an inhalation product].

This regularly used chemical becomes a novel excipient due to the new method of administration, and as a result, authorities will probably ask for more information regarding its safety. This will also apply to compounds that are GRAS-designated [generally recognised as safe] and used as food additives. While there won't be any legal issues if these ingredients are used in medications for oral administration, using them in any other form of medication will change their status and make them unique excipients.

The use of well-known [but not always the best] excipients has been chosen by businesses as the simpler, less expensive alternative since there is a general dearth of information that effectively prevents the production of unique materials. The regulatory requirements for novel excipients are difficult and complex, which has an effect on how frequently those chemicals are used in the EU. Novel excipients are an uncommon species since so few businesses choose to incorporate them into their goods. As a result, several excipients used in commercially marketed goods were first used roughly 100 years ago. [16]

c) The presence of publicly accessible information.

It is difficult to find and/or find a lot of information on innovative excipients in pharmaceutical products [authorised or withdrawn] in the public domain.

On certain substances, there is only scant and erratic evidence. An opportunity to inform and clarify the regulatory expectations for toxicological testing of novel excipients has been lost since information about the types of studies and testing carried out for approved novel excipients 6 is typically not released. In particular, if a substance is used in a drug product that is intended to be administered through the same route as the one that has already been approved, a different pharmaceutical company may use it without having to provide the same level of documentation.

In order to identify novel excipients in medicines approved for use in humans and authorised in the centralised procedure, a study of the European Medicines Agency [EMA] website [www.ema.europe.eu] was conducted. Sections of the European Public Assessment Reports [EPARs] were reviewed. However, there were very few pharmaceuticals with novel excipients discovered. The modest number of centrally approved pharmaceuticals with innovative excipients demonstrates that there is a regulatory problem because of the more stringent and intricate requirements. The centralised process ought to have drawn a lot of submissions for drugs with novel excipients. However, even in the case of novel drugs, businesses would rather use widely used excipients than take the chance of an approval delay. A challenge-free evaluation of this strategy is warranted, at least in terms of the excipients. [17]

Novel excipient	Substance type	Function	Medicinal product
Sulphobutylether β-cyclodextrin sodium salt [SBECD]	Cyclodextrin	Stabilizer and solubilizer of the active substance	Vfend
Poluquatemium-1 **[** polyquad**]**	Quatermary ammonium salt	Preservative	Travatan DuoTrav
Versetamide	Diethylenetriamine pentaacetic acid bismethoxy-ethylamide	Ligand [chelating agent]	OptiMARK
Sodium triphosphate pentabasic [$Na_5P_3O_{10}$]	Chemical subastance [salt]	Buffering agent	n/a
Recombinant human hyaluronidase [rHuPH20]	Glycosylated single chain protein with up to 447 amino acids	Facilities absorption and dispersion	Mabthera

Table 2: Instances of substances that have been employed and assessed as new excipients in medicinal products authorized through the centralized procedure in the EU.

Overcoming challenges

The present regulatory framework in the EU does not support and encourage the development of novel excipients, a process that is both intricate and costly. Typically, newly introduced excipients in the market are more advanced in nature compared to their familiar and widely utilized counterparts. Similar to the development of novel active compounds, their development produces a significant amount of proprietary data that needs to be protected.

Manufacturers of innovative excipients therefore support a Master File system for the distribution of their data. IPEC Europe believes that the implementation of an Excipient Master Files [EMF] system by the EU could notably reduce the timeline for bringing innovative excipients to the market. [18]

The US Food and Drug Administration [FDA] and the Japanese Pharmaceuticals and Medical Devices Agency [PMDA] have already begun using EMF systems. The Japanese Ministry of Health, Labour and Welfare [MHLW] has advocated the utilization of their Drug Master File [DMF] system for both new and blended excipients. Additionally, the FDA has outlined four categories of DMFs for pharmaceutical components, including Type IV DMFs, which are designated for excipients, colorants, Flavors, essences, or materials used in their formulation [FDA, 1989]. Unfortunately, there is no such option available in the EU.

The safety assessment of novel excipients presents another obstacle in addition to the procedural one. In accordance with the current regulatory framework, extensive safety assessments for novel excipients are necessary, roughly identical to those needed for a new active drug. The whole battery of tests typically required for testing novel active compounds may not be necessary for all of the new excipients, though. The development of new excipients may be hampered by excessive testing that isn't necessarily essential. This 'overkill' approach to safety evaluation could be a hindrance.

Excipients that have received approval for use in foods [often classified as GRAS] or cosmetics may not consistently demand the same battery of tests as entirely new substances. Novel excipients can encompass various types, including alterations to approved excipients, blends of existing excipients processed together, approved excipients suggested for new administration routes, and established excipients. Establishing the safety of co-processed excipients, for example, should be achievable by connecting it to the safety profiles of its constituent

components. This is because co-processed excipients are inherently designed without introducing new covalently bonded molecules. A toxicological evaluation shouldn't be required in the absence of a significant chemical change. The application of novel excipients may be encouraged and facilitated by clear guidelines and the ability to use bridging approaches for toxicological evaluation. [19]

Need of novel excipients:

The food industry has until now been an extension of the excipients sector. Excipients are also products of the food industry, which has contributed to their high level of safety. The International Pharmaceutical Excipients Council [IPEC], a global organisation, was created as a result of increasing regulatory pressure on the purity, safety, and standardisation of excipients. [20] The absence of any introduction of new chemical excipients into the market for a significant period indicates that the development of novel excipients has predominantly followed a market-driven approach, where excipients are created in response to existing market demand. This contrasts with a marketing-driven approach, where excipients are developed first, and market demand is generated through marketing strategies. [21] The comparatively high cost associated with excipient research and development is the main cause of this scarcity of new chemical excipients. However, there is increased demand on formulators to look for new excipients to accomplish the needed set of functionalities due to the expanding number of new pharmacological moieties with different physicochemical and stability qualities. The following are justifications for creating novel excipients:

1. Effective use of existing excipients: As opposed to a completely new development, finding new uses for the existing excipients is a procedure that takes less time and is substantially less expensive. One of these currently used excipients that has recently discovered new uses is chitosan. A new excipient that was created based on the coprecipitation of chitosan and silica and can be utilised as a super disintegrant is modified chitosan with silicon dioxide with improved flow and compaction properties. It also acts as filler. [22]
2. Excipients with desirable properties: Existing excipients differ in a number of ways from what is optimal for some formulations, such as soluble tablets, where the ideal lubricant should be water soluble and function similarly to magnesium stearate.
3. Drugs developed by genetic engineering: It can be difficult to predict how new medications will interact with excipients that are already on the market. Therefore, in order to solve these issues, new excipients will be required. When opposed to traditional oral solid dosage forms, medicines in the protein and peptide class need stabilisers of a different kind.
4. 4. Innovations in manufacturing methods and machinery: The evolution of pharmaceutical equipment and processes, particularly the capacity to produce at competitive prices and higher production rates, necessitates the development of new excipients. Unlike older machines that relied on materials with favorable flow characteristics, modern tablet machines demand materials with enhanced compressibility due to their shorter dwell and contact times.
5. Patient or subject adherence: Some of the excipients currently in use may not be suitable for patient comfort and safety. Individuals with lactase deficiency, for instance, may experience lactose intolerance, leading to symptoms like bloating, diarrhoea, and abdominal discomfort.

6. Specialized drug delivery systems: Special excipients are needed for the creation of unique or specialised drug delivery systems. Excipients of a specific size grade are required for metered dose inhalation devices, and the creation of mucoadhesive preparations required the use of novel bio adhesive polymers. [23]

Types of New Excipients

There are essentially three different types of excipients, and each of these has a distinct development process:

1. Modified Excipient [physical or purity changes]
2. Co-processed Excipient [excipient formulations]
3. Novel Excipient [new chemical entities].

1. Modified Excipient: An excipient's chemical composition, physical makeup, and properties, in general, define its characteristics. The toxicological properties and safety depend on the chemical makeup and structure. They are therefore difficult to change. The physical characteristics can be changed and tailored for particular uses, though. Particle size, morphology, and structure are a few examples of typical physical characteristics. These frequently vary. As a result, a variety of fillers, including lactose, mannitol, and microcrystalline cellulose, are available in various grades and each has advantages in particular uses and dosage forms.[24] As a result of stricter regulations for excipients based on pharmacopoeial monographs and government directives, product quality has increased. Customers are now requesting unique grades of well-known excipients for specific medications and dosage formats. Purity may be important in this context since undesirable reactive components may result in medication instability. A modification in an excipient's particle structure may make it easier to handle and enhance its qualities that are relevant to applications.[25]

2. Co-processed Excipient: In order to accomplish specific properties of a medication formulation, mixtures of excipients are frequently required because one excipient is simply insufficient. Thus, it is possible to mix a number of well-known materials in a way that results in the creation of new and/or superior physical qualities; as a result, they interact synergistically. However, in this instance, straightforward physical mixing is insufficient to achieve the excipient formulation's performance. These so-called "coprocessed" excipients are made of two or more compendial excipients that have undergone minimal chemical modification during formulation. [26-28] As a result, a coprocessed excipient's safety profile will often be the same as a matching physical mixture. Mixer granulation, fluid bed granulation, spray formulation, and microencapsulation are examples of common manufacturing techniques. Coprocessed excipients frequently make the production of pharmaceutical goods easier. Due to the improved process efficiency and decreased testing and documentation needs due to the use of fewer excipients, their use can save manufacturing costs. When appropriate, they even permit the Reduce the quantity of manufacturing steps required to create a dosage form. They are frequently employed for coating and direct compression applications, which facilitate and expedite the development of new drugs and their manufacture. [29, 30]

3. Novel Excipient: ICH Directive An excipient is deemed novel by M4Q if it is employed in a drug product or a new route of administration for the first time. Consequently, any excipients having a fully novel chemical structure or one Novel substances that haven't been seen before or utilized previously need to be thoroughly characterized with an emphasis on physiochemistry [including impurities and stability] and safety. Since these excipients are substances that have never been used on people previously, their comprehensive

toxicological characterization is necessary to establish their safety.[31] Even if the substances are well known, biotechnologically or biologically produced chemicals like albumin [Recombumin®] or transferrin [CellPrime® Transferrin AF] are nonetheless regarded as innovative excipients.

The creation and application of novel excipients is prompted by formulation difficulties that cannot be resolved by using already available materials or formulation techniques. The enhancement in bioavailability of poorly soluble or weakly permeable medicines is the most notable example.

Main Types and Examples of New Excipients:

TYPES	EXAMPLE
1. Modified Excipient	Tween™ 80 HP [Croda] Polyplasdone® Ultra [ISP] Kollidon VA 64 Fine [BASF] Swelstar™ Mx1 [Asahi Kasei] GalenIQ™ 721 [Palatinit]
2. Co-processed Excipient	Spectrablend™ HS [Sensient] Prosolv® ODT [JRS] Ludiflash® [BASF] Aquarius® [Ashland]
3. Novel Excipient	Kollicoat® IR [BASF] Soluplus® [BASF] Kollicoat® Smartseal 30 D [BASF] Captisol® [CyDex]

Table 3: Types of New excipients

Development of novel Excipients:

The most challenging aspect within these three categories is the development of novel excipients classified as new chemical entities [NCEs], a process that can span a minimum of 6-7 years and entail substantial costs. It's crucial to differentiate between two distinct types of developments: one where a new product is an extension or successor of a well-established excipient, and the other where the product is entirely original and has no prior equivalent. For instance, sulfobutyl beta-cyclodextrin [CAPTISOL®] and hydroxypropyl beta-cyclodextrin fall into the first category as derivatives of the well-known and approved beta-cyclodextrin.[32] However, this substance has significant disadvantages, especially with specific routes of administration, such as limited water solubility and hazardous effects when administered parenterally. By beginning Such shortcomings can be overcome and new qualities can be introduced by altering functional groups. When the substance is supplied parenterally, the substituted beta-cyclodextrin derivatives demonstrate a substantially better solubility in water, reducing nephrotoxic effects brought on by precipitation in the kidneys. Additionally, compared to the unmodified beta-cyclodextrin, the novel derivatives have a better solubilization capability for a variety of medicines. The second kind, the creation of a novel excipient in the absence of a basic structure, must begin with a screening phase to identify the best candidate.

In general, screening, product and process optimization, scale-up, toxicity research, and documentation make up the primary stages of developing novel excipients. The scope of toxicological research is essentially the same as that for a brand-new active component. Due to the involvement of numerous units—such as the polymer laboratory, production, process engineering, regulatory affairs, marketing, and toxicology—similarities also exist with regard to

the way development is carried out. These units should all work together as a project team.

Other factors, such as environmental concerns, manufacturing safety, c-GMP production, product safety, and prices, are also important in addition to a novel excipient's application-related performance.

Customers need monographed excipients or at least samples of medications containing the novel excipients in the relevant markets in order to reduce the risk of new drug discoveries, which is the conundrum that all developers of novel excipients must overcome.

It also implies that the project is not finished just because a new excipient has been introduced. Additionally necessary are getting medication licenses in the appropriate markets and adding monographs for novel excipients to the pharmacopoeias. The length of time needed by pharmaceutical companies to create and file new medication applications containing innovative excipients might be estimated to be between 3 and 4 years. The profitability of novel excipients is significantly reduced by these lengthy development timeframes, making such advances less desirable. [33]

Example of Novel Excipients:

1. Soluplus:

Because many novel active pharmaceutical components are poorly water soluble, solubility enhancers are one option for overcoming medication dissolution and absorption barriers in oral drug delivery. The efficacy of a novel solubility enhancing excipient [Soluplus] to improve intestinal medication absorption was investigated in this study. Danazol, fenofibrate, and itraconazole, BCS class II drugs, were examined in vivo in beagle dogs and in vitro in transport tests through Caco-2 cell monolayers. Each drug was used as a pure crystalline material, in a physical mixture with Soluplus, and as a solid drug solution in the excipient. In animal trials, the solid solutions of medication in Soluplus had a several fold increase in plasma AUC when compared to the respective pure drug. For fenofibrate, an effect of Soluplus in a physical mixture with the medicine could be detected. In vitro transport tests demonstrate Soluplus's considerable effect on the absorption behaviour of the three medicines examined. Furthermore, increased drug flow through the Caco-2 monolayer correlates with increased plasma AUC and Cmax in vivo. Soluplus has a high potential to improve oral bioavailability for these poorly soluble compounds. Caco-2 monolayers were found to be a useful tool for predicting the in vivo transport behaviour of model pharmaceuticals when combined with a solubility increasing excipient. Caco-2 studies also appropriately indicated the improvement of a solid dispersion over physical combinations of the medicines and excipient. In the case of fenofibrate, the potential benefit of a physical mixture was demonstrated, highlighting the utility of the used technology as an alternative to animal trials. [34]

2. Eudracap:

A chronotherapeutic drug delivery system [ChrDDS] containing montelukast sodium was created and developed to control early morning symptoms of nocturnal bronchial asthma using non-saccharide, totally synthetic Parteck® SRP 80 and hydrophilic cellulose derivative hydroxypropyl methylcellulose [HPMC]. A "tablets in a capsule" system including more than one compressed coated tablet encapsulated in an enteric-coated capsule can accomplish recurrent lag phases, each followed by the release of a fraction of the drug dose. The compression coating of HPMC K4M and a combination of ethyl cellulose and Carbopol polymer regulated lag time in this study. The system is made up of two compressed coated tablets encapsulated in a capsule, which was then enteric coated in a traditional, a unique wax-based, and a

EudracapTM enteric-coated capsule. The optimised formulation of immediately compressed Parteck ® SRP 80 tablets demonstrated a hardness of 8.8 kg/cm2, which is 1.25-fold higher than wet granulated HPMC tablets. Parteck® SRP 80 matrix tablet in vitro release study indicated regulated drug release for up to 10.8-11 h with various polymer and filler ratios. The minimum acid absorption value of EudracapTM capsule was 1.75%.The current strategy may pave the way for time-regulated montelukast release, which may be advantageous for people who have asthma attacks predominantly in the morning. [35]

Regulation for novel excipients:

United State of America:

The US FDA has provided guidelines on non-clinical studies for new excipients to determine their suitability for use in medication dosages with the label Non-Clinical Studies for the Excipients for Pharmaceuticals:

Safety Assessment. The Guidance aids in determining a chemical's safety for In an excipient, utilise. The designer of a new or The safety information should be developed by a novel excipient. recommended in these recommendations, according to their intending to use. The advice is focused on the creation of safety guidelines to facilitate the usage of new Excipients as pharmaceutical or biological ingredients products.

1. **For OTC product:** Per 21 CFR 330.1[e], the product should exclusively consist of appropriate inactive components that, when administered, are deemed safe and do not hinder the product's effectiveness or the validity of appropriate tests and assays to establish if the product aligns with its claimed standards for identity, potency, quality, and purity. The utilization of color additives is only permissible in compliance with subchapter A of this chapter and section 721 of the act.
2. **For Generic product:** Except for buffers, antioxidants, and preservatives, the USFDA mandates that generic drug products intended for parenteral, ophthalmic, or otic administration must incorporate the same excipients in identical concentrations as the reference listed drug product. This is contingent on the applicant identifying and delineating any differences while also providing evidence that demonstrates these disparities do not compromise the safety of the proposed drug product. In contrast, there is no stipulation requiring that excipients in the final formulations for other routes of administration, such as topical dermal or oral, match those in the reference listed drug product. Nonetheless, the applicant is obliged to demonstrate that the inactive ingredients do not have an adverse impact on the safety or efficacy of the proposed drug product.
3. **New Drug or Biological Product Application:** The essential supporting data for new products can be included within the application itself or submitted through a Drug Master File [DMF]. [36]

Novel Excipient Evaluation Procedure:

An expensive investment is needed to bring a novel excipient to market, hence they are not being used in pharmaceutical goods. For their formulation requirements, the majority of medication makers rely on excipients that have already been approved for use in drug products. Novel excipients are only examined as part of the drug application that contains them under the current drug approval procedures. A new excipient cannot be approved by the regulatory body as a standalone chemical. The IPEC Novel Excipient Safety Evaluation Procedure was conceived and created in 2007 by the IPEC-Americas Safety Committee.

It was anticipated that this independent excipient review procedure would lower the expense and

uncertainty associated with the use of novel excipients in pharmaceutical formulations, encourage their use in drug-development programmes, and give drug formulation innovation the much-needed boost. The Novel Excipient Evaluation Committee [NEEC], an independent expert committee of IPEC tasked with conducting the safety studies of new excipients, is managed by the Aclairo Pharmaceutical Development committee [Aclairo PDG, Vienna, VA]. The review panel has successfully reviewed Solutol HS 15 and is currently evaluating more products. [37]

Need of novel excipients:

The food industry has until now been an extension of the excipients sector. Excipients are also products of the food industry, which has contributed to their high level of safety. The International Pharmaceutical Excipients Council [IPEC], a global organisation, was created as a result of increasing regulatory pressure on the purity, safety, and standardisation of excipients. [38]

The absence of any new chemical excipients entering the market in recent years indicates that the development of novel excipients has primarily followed a market-driven approach, where excipients are created in response to existing market demand. This contrasts with a marketing-driven approach, where excipients are developed first, and market demand is generated through marketing strategies. [39]

The comparatively high cost associated with excipient research and development is the main cause of this scarcity of new chemical excipients. However, there is increased demand on formulators to look for new excipients to accomplish the needed set of functionalities due to the expanding number of new pharmacological moieties with different physicochemical and stability qualities. The following are justifications for creating novel excipients:

1. Effective use of existing excipients: As opposed to a completely new development, finding new uses for the existing excipients is a procedure that takes less time and is substantially less expensive. One of these currently used excipients that has recently discovered new uses is chitosan. A new excipient that was created based on the coprecipitation of chitosan and silica and can be utilised as a super disintegrant is modified chitosan with silicon dioxide with improved flow and compaction properties. It also acts as filler. [40]
2. Excipients with desirable properties: Existing excipients differ in a number of ways from what is optimal for some formulations, such as soluble tablets, where the ideal lubricant should be water soluble and function similarly to magnesium stearate.
3. Drugs developed by genetic engineering: It can be difficult to predict how new medications will interact with excipients that are already on the market. Hence, to address these challenges, the need for novel excipients arises. Unlike conventional oral solid dosage forms, medicines within the protein and peptide category necessitate a distinct type of stabilizers.
4. Progress in manufacturing techniques and equipment: The evolution of pharmaceutical machinery and processes, particularly in terms of enhanced production rates at competitive costs, necessitates the development of new excipients. Unlike older machines that required materials with favourable flow characteristics, modern tablet machines demand materials with improved compressibility due to their shorter dwell and contact times.
5. Ensuring patient or subject adherence: To ensure patient comfort and safety, several currently used excipients are not suitable.

Individuals with lactase deficiency may experience lactose intolerance, leading to symptoms like bloating, diarrhea, and abdominal discomfort.

6. Specialized drug delivery systems: Special excipients are needed for the creation of unique or specialised drug delivery systems. Excipients of a specific size grade are required for metered dose inhalation devices, and the creation of mucoadhesive preparations required the use of novel bio adhesive polymers. [41]

Advantages of Novel Excipients:

1. Increased drug bioavailability and solubility: New excipients can make poorly water-soluble medications more soluble and bioavailable. This is crucial for medications whose solubility in water is low.
2. Improved drug stability: New excipients can shield medications from damage caused by oxidation, light, heat, moisture, and other causes, extending their shelf life.
3. Controlled drug release: Excipients may be used to modify the active pharmaceutical ingredient's rate of release, enabling prolonged or precise drug delivery. This is advantageous for medications that need a certain release profile.
4. Taste masking and odour control: Excipients can be used to hide some medications' harsh or bitter tastes, making them more tolerable for patients. They can also regulate the smell of some formulations.
5. Reduced side effects and increased patient compliance: New excipients can lessen the negative effects connected to some medications, which can improve patient compliance with prescribed treatment plans.
6. Compatibility with various dosage forms: These excipients are adaptable for formulation development and can be used with a variety of dosage forms, including tablets, capsules, liquids, gels, and more.
7. Effective production processes: By optimizing powder flow characteristics, cutting processing times, and increasing the homogeneity of the finished product, some innovative excipients can streamline manufacturing procedures.
8. Better targeting and distribution of drugs to specific sites: Excipients can be developed to help drugs target to certain tissues or cells, enhancing the therapeutic benefit while reducing systemic side effects. [42]

Disadvantages of Novel Excipients:

1. Lack of existing regulatory guidelines or monographs may apply to novel excipients, making it more difficult to get regulatory approval for new medication formulations using these excipients. The process of developing new drugs may be delayed as a result.
2. Concerns about safety: Especially over the long term, the safety profile of novel excipients may not be well recognized. It's possible that the drug's active ingredient or other excipients have unintended negative effects or interactions that won't be discovered until after extensive testing or after the product has been sold.
3. Source variability: Finding new excipients can be harder than finding old excipients. The consistency and efficacy of medicinal products may be impacted by batch-to-batch changes caused by differences in the quality and availability of these excipients.
4. Cost factors: Creating and obtaining innovative excipients may be more expensive than using excipients that are more widely used. This might affect the final product's affordability by raising the overall cost of drug development and production.

5. Manufacturing difficulties: Novel excipients can call for specific equipment or manufacturing procedures, which could raise prices and complicate production. To include these excipients in their formulations, manufacturers might need to make investments in new hardware or software.
6. Compatibility problems: It can be difficult to predict how novel excipients, drug compounds, and other excipients will interact with one another, and it may be necessary to conduct comprehensive compatibility studies. Incompatibility may result in unstable formulations or diminished medicinal efficacy.
7. Intellectual property issues: Creating exclusive, innovative excipients can be expensive, and preserving the intellectual property relating to them can be difficult, particularly if other businesses or researchers independently develop excipients that are comparable to them.
8. Limited historical data: Due to the novelty and innovation of novel excipients, there may be little historical information on their performance, stability, and safety. Because of this, determining the long-term hazards connected to their use might be challenging. [43]

Applications of Novel Excipients:

1. Improved Solubility
2. Sustained and control release
3. Taste Masking
4. Drug Stability
5. Enhanced Drug Targeting
6. Incorporation of Biologics
7. Gene Delivery
8. Nano Particle formulation
9. Personalised Medicine
10. Modified Released System
11. Oral Thin Film
12. Nano medicine
13. Vaccine Formulation [44]

CONCLUSION

In conclusion, the world of pharmaceutical formulation is on the brink of a remarkable transformation, thanks to the ever-expanding array of novel excipients. The applications, advantages, and limitations of these novel excipients have been explored in this review, highlighting their pivotal role in shaping the future of pharmaceuticals. Their utilization not only enhances drug efficacy and patient compliance but also paves the way for tailored therapies that address individual needs more effectively. In essence, the incorporation of novel excipients represents a crucial step towards safer, more effective, and patient-centric pharmaceuticals. As research and development in this field continue to advance, we can anticipate an exciting era of pharmaceutical innovation, where the boundaries of drug formulation are continually pushed, bringing us closer to achieving the ultimate goal of improving human health and well-being

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