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A REVIEW ON EXCIPIENTS

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ABSTRACT

Different excipients are categorised according to the tasks they perform, for example, binders, diluents, lubricants, disintegrating agents, plasticizers, and so on. Excipients with therapeutic properties such as analgesics and sedatives are also included. Inert substances (excipients) are considered inert by the pharmaceutical industry. However, excipients can have the potential to reactwith medication components and packaging. An excipient must possess ideal qualities such as chemical stability, non-reactivity, low equipment and process sensitivity and non-toxicity.

KEYWORDS: Pharmaceutical industry, binders, diluents, lubricants, disintegrating agents.

INTRODUCTION

In today's pharmaceutical industry, many dosage forms are complex systems containing many other components in addition to the active pharmaceutical ingredient (API); these compounds are typically added in order to Protect, support, or enhance stability of the formulation:- It is commonly observed that the active pharmaceutical ingredient in its pure form does not retain its stability.- In the event of a strong medication, it is necessary to bulk up the formulation in order to help in the creation of an appropriate dosage form. Improve the level of patient acceptability. Improve the bioavailability of the active pharmaceutical ingredient: Excipients, such as ascorbic acid, are often used to increase the bioavailability of active pharmaceutical ingredients, such as ascorbic acid. An excipient is a material that is dissolved in or combined with an active component in order to facilitate the absorption of the active ingredient by the human body. Excipients may serve as a solvent or aid in the absorption of the active ingredient by the human body in many instances, such as aspirin. Improvements may be made to the overall safety and efficacy of the formulation while it is being stored and used. They are referred to as excipients in the pharmaceutical industry, and according to the International Pharmaceutical Excipient Council, an excipient is defined as "any substance other than an active drug or a prodrug that is included in the manufacturing process or that is contained in finished pharmaceutical dosage forms." Similarly, the United States Pharmacopoeia-National Formulary (USPNF) categorises excipients according to the roles they serve in formulations, such as binders, disintegrants, and other similar substances. Excipients maybe divided into three categories based on their origin, their usage in dosage form, and the roles they serve. These are as follows:

1. Excipients classified according to their origin5 Animal sources include lactose, gelatin, stearic acid, bees wax, honey, musk, lanolin, and other substances.

Vegetable sources include: starch, peppermint, turmeric, guar gum, arginates, acacia, and otherherbs and spices. Mineral sources include: calcium phosphate, silica, talc, calamine, asbestos,kaolin, paraffin, and other substances with a phosphate content. Boric acid, saccharin, lactic acid, polyethylene glycols, polysorbates, povidone, and other synthetic compounds are examples.[2] The following tables provide a categorization of the different excipients used in pharmaceutical dosage forms, which includes the following:

Classification of excipients based on their functional characteristics[10-13]: - Excipients are categorised according to the tasks they perform, for example, they are classed as follows: Different excipients used in solid dosage forms perform different functions, such as:- binders, diluents, lubricants, disintegrating agents, plasticizers, and so on. For example, when 5 percent starch is used in formulation, it acts as a binder for tablet formulations, whereas when used in dry form, itperforms the function of a disintegrant. Excipients that are utilised in liquid dosage forms include:- solvents, co-solvents, buffers, and other additives. Agents that are

anti-microbial the agents that emulsify sweetening agents, flavouring agents, and so on There are many excipients with therapeutic properties, which are categorised as follows: - Analgesics and sedatives 10:- chloroform and other chemicals Laxatives such as bentonite, psyllium, xanthan gum[11], guar gum, and othersare available. Citric acid is one of the ph modifiers. Cinnamon, alum, zinc sulphate are all astringent ingredients. Cinnamon[13], dill water, and anise water are carminative in nature. Sources of nutrients include agar[12], lactose, and other sugars. Selection of excipients for[14]:- Excipients are considered to be an indispensible component of pharmaceutical products, and in most formulations, they are present in greater proportion to the active pharmaceutical ingredient than the active pharmaceutical ingredient. Because excipients constitute the majority of the formulation, it is always necessary to select an excipient that has the ideal properties for a particular excipient. Excipient selection is typically guided by desired properties of excipients, such as functionality, material consistency, regulatory acceptability, cost, availability, and source(s) of supply. In the creation of medication formulations, material characteristics such as micromeritics, chemical thermal rheology, mechanical properties, and so on, are also essential considerations to consider. When selecting an excipient for formulation development, formulators should take into account physicochemical properties, stability and compatibility issues, pharmacokinetic attributes, permeation characteristics, segmental absorption behaviour, drug delivery platform, intellectual property issues, and other factors. This will assist formulators in determining the absorption challenges and desired delivery platform for active pharmaceutical ingredients. With the idea of quality by design (QbD), it is possible to get a better knowledge of excipient normal variability and its potential effect on the formulation development processes. It is possible to identify medication excipient interactions that may be avoided or changed to allow for more efficient use of the excipients. This assists in reducing the riskassociated with the use of the excipients. The choice of excipients is also influenced by the different administration routes. The selection of excipients must be made on the basis of the qualities that each excipient has and does not possess. The following are the qualities of an excipient that are considered ideal:- In order to be acceptable, an excipient must possess the following qualities:- Chemical stability; non-reactivity; low equipment and process sensitivity; non-toxicity; and acceptability with features. In terms of organoleptics, it is cost-effective. Having high efficiency when it comes to the intended use. However, despite their status as inert substances, excipients have the potential to react with medication components, other excipients, and even the packaging system itself. It is also possible that excipients include contaminants that cause the breakdown of the active medicinal components in a formulation and therefore reduce the shelf life of that formulation. In thepharmaceutical industry, the different types of interactions that an excipient may have with a drug are referred to as drug-excipient interactions. Excipient-excipient interactions are important. Interactions between the package and the excipient The following interactions are explored in more depth:- Drug – Excipient interaction[15-19] Medicinal dosage forms come into close contact with the excipients, which are present in larger quantities than the active pharmaceutical components. When specific incompatibilities exist between excipients and medicines, this may result in a drug– excipient interaction.

It is possible that excipients may alter the physicochemical characteristics of the active pharmaceutical component, resulting in the formation of molecular complexes, an increase in the rate of chemical degradation, and other undesirable effects. Drug excipient interactions are further subdivided into the following categories: Physical interactions Chemical interactions Biopharmaceutical interactions Physical interactions: Physical interactions affect the rate of dissolution, dose homogeneity, and other aspects of the drug's effect. It is because physical interactions do not result in chemical changes that it is possible to keep the molecular structure of the components in the formulation intact. Physical interactions are notoriously difficult to detect and characterise. Because of this, physical interactions may be helpful or harmful to the effectiveness of a product, depending on the application. Table No. 4 contains a list of many kinds of physical interactions, including The following are examples of chemical interactions: - active pharmaceutical components and excipients react with one another, forming unstable molecules. Excipient interactions with chemical medicines have been documented in the literature on many occasions. Chemical interactions, in general, have a negative impact on the formulation, and as a result, such interactions should be avoided wherever possible. Several instances of chemical interactions are given in Table No 5. After administration of the drug, biopharmaceutical interactions are detected, and these interactions are classified as follows: Interactions inside the body occur between medication and bodily fluids, and these interactions have an impact on the rate of absorption. When excipients are given in conjunction with active medicinal substances, they all interact in a physiological manner. The following are some instances of biopharmaceutical interactions: 1) An early disintegration of the enteric coat: Because the soluble polymers in enteric coatings such as cellulose-acetate-phthalate and hydroxypropyl-cellulose-acetate-phthalate are more soluble at basic pH, antacids raise the pH of the stomach, causing the breakdown of the enteric coat in the stomach and the release of the active pharmaceutical ingredient in the stomach itself, resulting in drug degradation. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may result in the early disintegration of the enteric coat, which may result in gastric bleeding. Adjunctive therapy-induced interactions are discussed below. When tetracycline antibiotics are combined with calcium and magnesium ions (which are often found

in a variety of formulations and may be given with tetracycline as adjunct treatment), the complex produced is not absorbed from the G.I.T. (gastrointestinal intestinal tract). 3) Enhance in gastrointestinal motility: - Many excipients, such as sorbital and xylitol, have the potential to increase gastrointestinal motility, thus decreasing the amount of time available for the absorption of medicines such as metoprolol in the body. Ranitidine absorption is also affected by the presence of polyethylene glycol 400 in the solution. d. Interactions between excipients and excipients[19,20,21,22,23,24,25, and 26]: Though very rarely seen, excipient-excipient interactions play a critical role in regulating the stability of dosage forms, particularly in the case of aqueous solutions. Interactions between excipients and excipients may be undesired, while certain interactions are utilised in formulations to achieve the desired product characteristics. Various excipients are subjected to this kind of interaction. Table 6 15 contains examples of unfavourable excipient-excipient interactions that should be avoided. To achieve the intended effect in the product, certain excipients are formulated as a combination; for example, some excipients are combined with other excipients. interactions between excipients and excipients are helpful for enhancing the functional performance of the formulation when used together Coprocessed excipients are a kind of excipient that is used in conjunction with other excipients. Compounding excipients: - Tablets are usually regarded the dosage form of choice when the oral route is chosen, owing to the accuracy of dosing and improved patient compliance that they provide. Excipients such as binders, disintegrants, diluents, glidants, and lubricants are used in the production of pharmaceuticals.

etc. are employed in conjunction with the active pharmaceutical ingredient during the tablet production process. These excipients aid in the enhancement of different dissolving, absorption, and other characteristics of the active pharmaceutical component when the tablet is manufactured, for example. A number of excipients are unable to provide the required results; as a result, the need for modified excipients with improved characteristics is identified and created. It is a novel concept thathas been introduced, and its functionality is to alter the excipient by retaining favourable attributes while adding newer ones, by processing the parent excipient with another excipient. Co processing is a novel concept that has been introduced, and its functionality alters the excipient by retaining favourable attributes while adding newer ones. The high functionality excipients that are produced as a result of this method assist to enhance process ability, such as flow properties, compressibility, and better disintegration and dissolution profiles, among other characteristics. Tablet production is being challenged by the introduction of high-speed tablet machines and direct compression methods, which are posing a number of challenges. Because of their multifunctional characteristics, co processed excipients are useful in the solution of such issues. Co-processing offers a synergy of functionality enhancement while also concealing the negative characteristics of separate excipients, resulting in a more effective product. The goal of co-processing is to improve flow characteristics, compressibility, disintegration potential, and the creation of filler-binder combination materials. Asa result, many bulk excipients used in traditional tablets are inappropriate for use in orally disintegrating tablets, necessitating the employment of specialised excipients and technology to conceal the drug's undesirable taste while also improving the orally disintegrating tablet's characteristics. The capacity of the excipient to absorb water rapidly contributes to the rapid impact of dispersion on the environment. The use of superdisintegrants such as crosspovidone sodium, starch glycolate, and crosscarmellose in tablet formulations also aids in the dispersion of tablets on the tongue's surface. For orally disintegrating tablets, mannitol has been modified to provide additional functionality. Directly compressible mannitol is commonly used because of its ability to produce robust tablets. Spray dried or directly compressible mannitol, on the other hand, is highly porous and friable, and upon compression, fills the interstitial spaces between larger porous particles. Although orally disintegrating tablets have the drawback of being very friable, co- processing of mannitol with certain polyols may provide comparable flowability and compressibility with the added benefit of reduced friability when compared to straight compressed mannitol (see Figure 1). f. Pregelatinized starches provide additional functionality by being used as filers in hard gelatin capsules (5-75 percent), binders in wet granulation tabletting (5-20 percent), disintegrants in tablet formulation (510 percent), and also in direct compression tablets, which also provide better particle size control, decreased friability, narrow particle size distribution, and lower levels of fines, among other things. When formed of tightly linked starch particles, partially pregelatinized starch particles with compact, embedded matrix are considerably less friable than when produced of loosely attached starch particles. Medications such as acetaminophen, for example, benefit from the fast dissolving of partly pregelatinized starches in a compact matrix formulation. Table 7 g contains some examples of excipients that are used in pharmaceutical manufacturing. interactions between excipients.[28-31] in the package: A determination of a product's physical and chemical characteristics, as well as its protective needs and marketing requirements, is necessary before selecting a packaging solution for it. - Pharmaceutical packaging is an important part of the product formulation process, and it is critical in the pharmaceutical industry that the packaging solution chosen adequately preserves the integrity of the product. The packaging so chosen should be non-reactive in nature, should shield the product from external environmental conditions, and so on and so forth. The most often used packaging materials include glass, plastic, metal, and rubber closures, among other things.

These containers and closures react to a certain degree with the drug product as well as with the excipient and cause detrimental effects, thus changing the product stability. In most cases, such interactions result in a reduction in product quality.

A critical role in ensuring the safety, quality, and effectiveness of dosage forms is played by the excipients used in their manufacture. Standardization of excipients typically provides customers and manufacturers with the assurance that the excipient quality will meet the standards of the international market; as a result, the rules for regulation of bulk excipients are stringent, and whenever a new excipient is to be introduced, it is necessary for the applicant to submit safety and quality data, and whenever an approved excipient is to be introduced, it is necessary for theapplicant to provide literature reference data. It is necessary to standardise excipients for many reasons. The most important of these is to provide assurance to the customer that the excipients being used are safe and will not change the formulation or produce unwanted effects. For the manufacturer to be confident in the knowledge that he is creating his dosage form with high-quality raw materials, and To minimise the number of resources required to host regular customer audits and to ensure that the excipient GMP audit is performed in accordance with acceptable GMP compliance standards. The ISO 9001 quality management system standard was selected as the basis for the quality management system. The ISO certification has the benefit of providing consumers with the assurance that the quality management system of the excipient manufacturer has been independently validated. GMP practise for excipients ensures product integrity and helps to prevent product contamination, among other things. IPEC is an international industry organisation that was established with the primary goal of developing and harmonising worldwide excipient standards, as well as developing novel excipients for the pharmaceutical industry. It deals with three types of stakeholder groups, namely, suppliers, users, and regulatory agencies, among others. It is necessary to obtain sufficient information about the excipient as well as the manufacturer or distributor; typically, in order to obtain such information as well as detailed information about the excipient, users and customers send questionnaires to the supplier; the questionnaire contains a large numberof questions that are difficult to resolve and address individually, resulting in a significant amount of time and money being wasted during this process; as a result, Overview of the site's quality, as well as an overview of the site's and supply chain security. This information is helpful in responding to surveys and other requests in a simpler and uniform manner, which is very beneficial in terms of time savings. This information is beneficial to both users and suppliers in that it allows them to handle information in a more organised and effective way. Product regulatory database: This document was created with the primary goal of providing information to the user about important physical properties, manufacturing processes, and regulatory information specific to excipients, in order to facilitate the use of excipients in drug formulations. Product regulatory database: The different parts that are included are as follows: Product identity, product code/name, scope of document, and any other information that is required are all included in the general product information section. The following information is provided in this section: manufacturing, packaging, product release, and supplier information. For example, manufacturing processing, packaging, product release warehousing, and laboratory site are all described, as well as distributionchannels, GMP or GDP compliance statements and information, as well as excipient manufacturing site equipment. Information on the physical and chemical characteristics of the product is contained in this section, which includes, for example:- the CAS number, information on the origin of excipients, their synonyms, the product's morphological characteristics, the processes used during manufacturing, information on mixed excipients, and the country of origin, if any. This section describes the regulatory status of an excipient and includes information such as compendia compliance (e.g. USP-NF, Food chemicals codex, BP, etc.), drug master file (or European Directorate for the Quality of Medicines and Healthcare (EDQM) certificate of suitability), viral safety, allergens and hypersensitivity information, residual solvent information, metal catalyst and metal reagent residue in excipients, and residual solvent information in a drug master file. Information on kosher/halal status, bioburden/pyrogen (optional) information, and so forth. Other product information that may be useful: - This part contains information such as the lot/batch number, expiration date, usage, nutritional information (if applicable), and so on.

Revision: This section contains information on how to maintain version control for a document or spreadsheet. In this area, you'll find the supplier's contact information. There are various sections that are included in this document, which are as follows: Site quality overview:- this document provides information regarding the manufacturing site, as well as any other areas related to excipient processing or testing. There are various sections that are included in the documentation, which are as follows: - Site overview: This part covers the organisation and production capabilities of the supplier; issues included in this area include the site name, location, corporate ownership, customers audit policy (optional), site information, and so on. In this section, information about the facilities being provided is described, such as ISO certification and GMP inspection by a competent authority, GMP statements and information about external audit programmes such as the International Pharmaceutical Excipients Auditing (IPEA), AIB international, GMASAFE, and others. Supplier compliance with IPEC-PQG GMP requirements:- This section contains information on how suppliers adhere to the relevant components of the IPEC-

PQG-GMP guide. Other site information:- here contains any extra information that has been given about the site (optional). Other information contains the company's contact information, among other things. Site and supply chain security overview:- This document contains information about the protection of the product and the continuity of supply as guaranteed by the supplier. This document includes information about the site name, address, evaluation of the carrier, tamper evident packaging, qualification of the distributer, broker, intermediate storage location, repackaging, relabeling activities, FDA registration information, security, safety, and other aspects of the supply chain, as well as information about the supplier. This helps to reassure the user, client, and supplier about theexcipient's quality, and it may also offer confidence that the process will continue to produce excipients of high and standard quality. - Excipient stability testing (excipient stability testing)33 The primary goal of compatibility testing is to identify the most suitable Excipient(s) for a certain API in the dosage form under consideration, as well as the Excipient(s) that should be avoided for a specific API in the dosage form under consideration. Excipients may be obtained from a variety of sources, including both natural and synthetic sources of origin. Natural sources of excipients are frequently contaminated with microorganisms and certain impurities, which can cause the formulation to become incompatible and therefore unable to be used; therefore, in order to avoid any incompatibilities in the formulation, the excipients must be tested for stability before use. To assist in the creation and harmonisation of international excipient standards, IPEC has established a set of recommendations for the stability testing of excipients with the goal of promoting international cooperation. Excipient manufacturers may use these recommendations to develop a stability research programme for their products, which will aid them in determining revalidation intervals or expiry dates for their excipient products. This study's major goal is to ensure that the excipient's stability is maintained during the production process, packaging, and until the package isopened. The stability studies are designed on the basis of the following factors: 1) the use of historical data about a specific excipient and the drawing of conclusions about excipient stability; and 2) the use of current data about a particular excipient and the drawing of conclusions about excipient stability. 2) Carrying out stability tests using excipients packaged in commercial packaging and storing them in various warehouses where the temperature is constantly monitored 3)Conducting research in accordance with the criteria and guidelines outlined in ICHQ 1A (R2): - These recommendations are intended to aid in the conduct of stability testing, which gives proof of the quality of pharmaceutical goods when subjected to a variety of environmental circumstances. The selection of test circumstances is based on the analytic impacts of climatic variables in three different areas, namely Europe, Japan, and the United States of America. In compliance with the guidelines, the following processes are carried out as follows: 1) Stress testing: It aids in the identification of degradation products present in formulations by exposing them to extreme conditions. Such testing is carried out in a single batch, and the impact of temperature is evaluated by increasing the temperature in increments of 100 degrees Celsius, for example, 500 degrees Celsius, 600 degrees Celsius, and so on. Above this temperature, accelerated stability testing is carried out. In order to conduct the testing process, the humidity must be maintained at or above 75% relative humidity (RH). Excipients are subjected to the conditions specified in ICHQ 1Bduring stress testing, and photo stability testing is an important component of the stress testing process. 2) Specifications: Specifications for analytical methods are followed in accordance with the established guidelines and standards

ICHQ 6A[9] and ICHQ 6B, as well as ICHQ 3A for degradation products, are all examples of international standards. Tests are performed every three months during the first year of storage, every six months during the second year, and yearly afterwards for long-term storage conditions. For accelerated stability tests, testing was performed at three different time points: 0 month, 3 month, and 6 month. It is usually advised to conduct testing over a period of six months. Conditionsfor storing the product: - excipients are subjected to storage conditions tests to determine their thermal stability, moisture sensitivity, and solvent loss. For storage testing, the following standards are required to be followed

Methods for determining stability include the following: - Excipients should be evaluated for stability utilising techniques such as stability indicating assays, microbiological, physical, and chemical testing, among others. Chemical stability may be determined using chromatographic techniques, while physical stability can be determined using microscopy, particle size analysis, in vitro dissolution experiments, and other methods. Different analytical methods, including as thermal analysis, chromatographic techniques, diffuse reflectance spectroscopy, and others, are employed inthe identification and evaluation of excipient compatibility, among other things. It is also important to consider the stability of excipients when comparing their composition profiles at the end of their retest/revaluation intervals (if applicable) to those of the excipients at time zero; the composition profile of the excipients should remain unchanged under the recommended storage conditions. Evaluation of the excipient's safety34 The IPEC New Excipient Safety Evaluation Method, which is an independent excipient assessment procedure, was created in 2007 by the IPEC-Americas Safety Committee and published in 2007. According to the method, expenses associated with superfluous testing and uncertainty associated with the use of novel excipients will be reduced, thus promoting their use in medication development and increasing innovation in the formulation of pharmaceutical products. Excipients are

evaluated for their safety using a variety of in-vitro assay methods toscreen for potential toxicity. By using this procedure, it is possible to eliminate materials that are known to cause unwanted toxicity. This procedure is developed in several tiers of testing, with the first tier testing for the compound's genotoxicity, cytotoxicity, metabolism, and the ability of the compound to cross biological membranes being performed. This phase may also involve the creation of QSAR research, which may aid in the prediction of the toxicity of certain substances. Following this first stage, further procedures such as testing for immunotoxicity studies, repeat dosage toxicity testing, safety pharmacology studies, and so on may be performed in the future. To begin, the excipient safety dossier (in Common Technical Document format) is submitted to Product Development Group, which then forwards it to the chairman of New Excipient Evaluation Committee (NEEC), who then distributes it to the other committee members. If possible, it is suggested that Excipient dossiers be produced in accordance with IPEC's Master File Guide. Part I of the file guide is broken down into two sections. The first part is the administrative portion, which varies from area to region depending on the details of the application and local regulations. The second document is the core technical document (CTD), which contains all of the technical information and summaries required for Excipient approval in the majority of locations, as well as the CTD P4 criteria. The reviews are anticipated to take between one and three months, depending on the amount of material included (or missing from) the dossiers throughout the review process. This will be based on no more than 50 hours of review time plus administrative overhead in the vast majority of instances. In this case, the chairperson or a designee gathers all of the committee members' opinions and writes a report, which is then given to each member for approval or additional debate. Once an agreement has been achieved, the completed report is sent to the excipient sponsor for review and comment before being released. If the expert committee is unable to reach consensus on one or more items in the final report, the sponsor is informed of the disagreements and the reasons for the differences. After reviewing the final report with the expert committee, the sponsor has the option of requesting clarifications or more information. Onceeveryone is happy with the final report, the chairman signs it and delivers it to the sponsor, who becomes the only owner of the final report after that. The report will include, at a minimum, the following information: 1. A discussion of chemical and toxicological data and human safety concerns based on the intended use of the excipient; 2. Opinions on conformance with data needs as defined by the CDER Guidance; and 3. Identification of data gaps, if any, and points of reviewer disagreement that were not resolved, as well as the reasons for these decisions. Excipient safety evaluation procedures such as the IPEC New Excipient Safety Evaluation Procedure are excellent methods for independently evaluating the safety of new excipients, including co-processed mixtures of existing excipients, physical and chemical modification of existing excipients, higher use levels of existing excipients, and NCEs. The report from the NEEC may be used by the excipient sponsor to support the adoption of a novel excipient during the drug development approval process. As novel excipients are introduced, it is critical to identify their potential use in a variety of complicated delivery systems, and the IPEC process assists in this endeavour.[35]

CONCLUSION

Excipients, which are essential components of pharmaceutical medicines, must be assessed for their safety and stability before being used in clinical trials. It is possible that the different excipient interactions, such as drug-excipient interactions, excipient-excipient interactions, and package-excipient interactions, will make the excipient unfit for use in formulation. The use of various stability testing procedures, in which the excipients are subjected to extreme temperatures, humidity, and other environmental conditions, is carried out in order to avoid the use of incompatible excipients and to ensure that the excipients are safe and stable for use in the formulation design process. The safety of excipients is further tested if the results of the stability testing indicate that they should be used in a formulation. Safety is the most important feature of any formulation intended for use in humans or animals, and it is the most important feature of any formulation intended for use in humans or animals. With the introduction of novel excipients, it is critical to identify their potential use in a variety of complicated delivery systems. The IPEC process ensures that new excipients with the potential to be used in humans undergo a comprehensive safety evaluation.

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