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A Review on Tablet in Tablet for Cancer and Use of Artificial Intelligence (AI)

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ABSTRACT

The tablet is the most commonly utilised dosage form because to its stability and high level of acceptance among patients. The film and sugar coatings have a crucial role in enhancing the aesthetic qualities of the tablet, such as colour, texture, mouth feel, and taste masking. Therefore, the coating is a vital component in the tablet formulation. Film and sugar coatings have several drawbacks, with the most significant being the use of aqueous or organic solvents, which can result in toxicity. In 1896, Noyes proposed the compression coating or Tablet in Tablet technology as a solution to this problem. The literature contains significant research reports and patents inputs that have garnered great attention from researchers in the development of Tablet in Tablet dosage form. Furthermore, our attention was directed on the latest progress in methodologies such as one-step dry-coating (OSDrC®) for the analysis of manufacturing properties. Additionally, we discussed the obstacles encountered in the creation of a Tablet in Tablet dosage form for cancer treatment. The present review compiled data on the most recent patent, use of artificial Intelligence for Tablet in Tablet or compression coating.

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Introduction

The tablet is the most often utilised form of medication due to its ease of administration, costeffectiveness in production, and aesthetic appeal [1]. The aesthetic attributes, such as colour, texture, mouthfeel, and flavour masking, are contingent upon the use of coating processes [2]. Currently, there is a low number of patents filed or granted on this topic. One example is the patent on the Tablet in Tablet of cyclophosphamide and capecitabine [3]. In this study, our attention was on the reasoning behind the invention of this particular dosage form. This review aims to emphasise the progress made in the production process of tablets and its advantages for the pharmaceutical business [4].

The coating provides both physical and chemical protection to the medicine, as well as altering the drug's release behaviour. In the nineteenth century, modern pharmacological coating, specifically sugar coating, was used to conceal the unpleasant taste [2,5]. Sugar coating has some problems and restrictions. It necessitates a lengthy processing time of up to 6 to 7 days and involves multiple steps such as sealing, subcoating, smoothing, colouring, and polishing. Skilled operators are necessary to perform these tasks.

To address the issue of film or sugar coating, the Tablet in Tablet or compress coating technology is introduced as an alternating coating method. It is also known as a dry coating or press coating and was one of the initial solvent-free coating processes. Typically, a tablet, whether it be a tablet in tablet or a compression-coated tablet, is composed of two components: an inside drug core and an external coating shell. The outer layer envelops the inner core and primarily governs the film coating's strength, drug release, and stability [6].

Benefits of Tablet in Tablet technology [2,9]

Incompatible materials can be separated within the core and outer shell.

It will be utilised to create a modified release product, such as a delayed release product [7,8]. The Tablet in Tablet technique can be employed to target two different medications to two distinct sections of the gastrointestinal tract. iii. The requirement for a distinct coating procedure for the tablets can be eliminated by utilising press coating for both the core and coating layer.

This coating does not include any solvents, making it environmentally safe. The Tablet in Tablet dosage form can prevent pharmacokinetic interactions between concurrently delivered pharmaceuticals by controlling their release time intervals.

The Tablet dosage form provides protection for hygroscopic or thermo-labile drugs.

A single tablet in tablet dose form can provide both immediate release and sustained release effects, whether using the same medicine or a combination of different drugs [9,10].

Challenges Pertaining to Tablet technology

The potential for cross-contamination between the layers.
The elastic modulus is not consistent between the adjacent layers.
The insufficient layer adhesion and comparatively weak interfacial strength are due to the high elastic modulus ratio between adjacent layers.

Encounter difficulties in maintaining the physical and chemical integrity of the device over an extended period of time during storage.

The tablet's enormous size causes difficulty in swallowing [4].
The discrepancy in coating effectiveness when the core tablet is not positioned at the centre of the system [11].

Review of Patents

The tablet contains a combination of cyclophosphamide and capecitabine. Cyclophosphamide is a prodrug that undergoes hepatic conversion to its active form, which exclusively inhibits the proliferation of cancer cells. The management of many types of diseases such as metastatic breast cancer, ovarian cancer, and leukaemia Cyclophosphamide can be used either as a standalone treatment or in conjunction with other medications. Capecitabine is a pharmaceutical agent employed in the management of metastatic breast cancer [12]. Additionally, the co-administration of capecitabine with another drug is crucial for the stimulation of the thymidine phosphorylase (TP) enzyme. This enzyme is responsible for converting capecitabine into its active form, 5-FU (fluorouracil).

Many practitioners have observed that the oral administration of cyclophosphamide plus capecitabine has a greater potential for managing metastatic breast cancer. The total impurity level exhibited a significant rise when these two therapeutic agents were administered together, mostly due to their incompatibility [13]. Consequently, the formulation of a stable oral composition containing both medications posed a considerable challenge. Cyclophosphamide is subject to hydrolysis and readily breaks down in the presence of water and light. It is also susceptible to high temperature. The aforementioned issue can be resolved by the creation of a single-unit stable oral dosage form known as Tablet in Tablet (US 20190142755) [14].

The tablet is the most popular and convenient solid oral dose form of all available options. Tablets are categorised into many forms. One class of tablet is the modified release dosage form, which is very important in drug treatments due to its numerous advantages. In contemporary times, the Tablet in Tablet technology (Fig. 1) is the most optimal choice for creating modified released goods, particularly for bilayer tablet formulation involving incompatible drugs. This process entails the compaction of granular substances around a preexisting tablet nucleus with specifically engineered tabletting machinery. The term "Tablet" in Tablet refers to a process called compression coating or solvent-free coating.

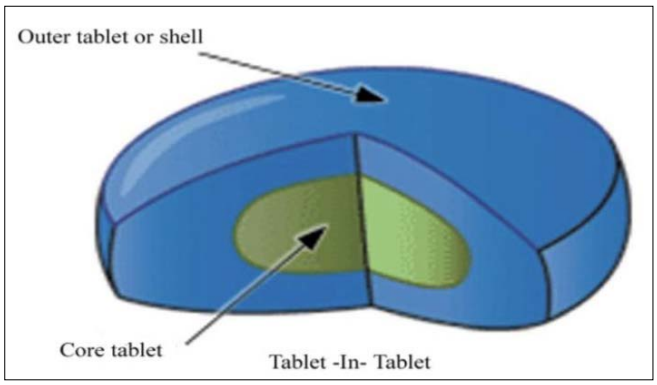

Figure 1: Tablet in Tablet Source: https://www.pharmaexcipients.com/news/tablet-in-tablet-techniques/

The Tablet dosage form consists of two components: the interior core and the outer covering. The internal core is a compact tablet that is manufactured using smaller tooling compared to the tooling used for the outer coat preparation. Once the internal tablet core is manufactured, it is placed in another die that is partially filled with coating powder. This die is larger than the core tablet. The remaining coating powder is then added on top of the core tablet and compressed, resulting in the formation of a tablet within a tablet [15]. This procedure can result in an issue where the core tablet may become skewed during its transfer to another die. In order to create a product that is released quickly, the coating is typically made to dissolve in water and break apart easily after being taken orally. The Tablet in Tablet can be employed for the formulation of controlled-release tablets, where the outer layer delivers the first drug dose while the inside core releases the drug at a later time. The repeated use of tablets in tablet dosage form poses a danger of overdose toxicity due to the fast release of the drug from the core tablet, resulting in varying blood levels [16,17]. The list of drugs produced in tablet form, namely as compressed coated tablets, is presented in Table 1

Table 1: List of Drugs that are Formulated in Tablet-in-Tablet

Active Ingredient	Category	Excipients	References
Paliperidone	Antipsychotic	HPC-H, Euragit RL-PO, Glycerylbehenate, MCC, HPMC-	[6]
Orlistat and Venlafaxine	Antiobesity and antidepressant	For core tablet—βCD, SD Mannitol, Ludiflash, Kollidon CLF, Kollidon-30, SLS, Sucrose, Talc, MgStearate, Cherry Flavour, Methyl Paraben	[18]

Amoxicillin and Potassium Clavulanate	Antibacterial and β lactamase inhibitors	Steric acid and avicel layer	[19]
Acetaminophen	Analgesic and antipyretic	HPMC, Mg.Sterate, Lactose-crystal cellulose	[20]
Glipizide	Antidiabetic	βCD, HPC-L, HPC-M, MCC, Eudragit RL PO, Mg.Sterate	[21]
Nifedipine	Antihypertensive, calcium channel blockers	HPC-L, HPC-M, Eudragit RSPO, Mg.Sterate	[15]
Prednisolone	Immuno-suppressant	Carboxymethyl xanthan gum, Sodium alginate, Calcium chloride, MCC,Polyplasdone XL, Tri-Sodium Citrate, Trisodium orthophosphate dodecahydrate, Mg.Sterate.	[22]
Carvedilol	Antihypertensive or non-selective beta adrenergic receptor blocker	Polyoxy Ethylene Oxide WSR 205, HPMC K4M, MCC, Sodium starch glycollate, Mg.Sterate.	[23]

Recent Advancements

The conventional dry-coating or Tablet in Tablet manufacturing processes, as shown above, can lead to issues such as non-core, double-core, off-center, and inlay, which are caused by the core tablet transit mechanism. Therefore, the utilisation of dry coating or Tablet in Tablet is not as prevalent as that of traditional tablets [24]. The key necessity in the indicated procedure is to compress the core tablet in advance, which will result in an increase in the overall production cost of the dosage form [25]. The introduction of revolutionary one-step dry-coating (OSDrC®) technology has revolutionised tablet manufacture by addressing issues associated with conventional dry-coating processes including Tablet in Tablet creation. The OSDrC® is a trademark that has been officially registered by Sanwa Kagaku Kenkyusho Co., Ltd., a company based in Japan. By manipulating the thickness of the outer coating layer formulation, scientists were able to exert control over the release of the drug [17].

Artificial intelligence (AI)in the development and formulation of cancer tablets

Artificial intelligence (AI) plays a crucial role in the development and formulation of cancer tablets. Here's how AI contributes across different stages of the process [26]:

Drug Discovery [27]

Identification of Targets: AI algorithms analyze biological data to identify new molecular targets for cancer therapy. This can help discover new drugs that target specific cancer cells.

Virtual Screening: AI can screen vast libraries of chemical compounds to predict which ones are most likely to bind to cancer targets effectively. This reduces the time and cost associated with experimental screening [28].

Formulation Development [29]

Predictive Modeling: AI models can predict the behavior of different formulations under various conditions, such as solubility, stability, and bioavailability. This helps in selecting the best formulation parameters. ii. Optimization Algorithms: AI can optimize the combination of active ingredients and excipients (inactive substances used as carriers for the active ingredients) to enhance the therapeutic effectiveness and reduce side effects

Benefits of OSDrC® [17]

This method enables precise control over the weight of each layer of the tablet by utilising a single-step operation, where both the tablet and core are produced in one rotation of the punches on the turntable. The innovative cam movement design and customisable double punch arrangement allow for the exact application of coatings of any thickness and tablet shape. Additionally, there is no need for a separate operation to make a core tablet. The technique is a single, solvent-free coating method. It produces high-quality tablets with precision, thanks to the design of a double punch that can move independently and vary in speed. This OSDrC® technology can be used to construct modified release formulations or drug administration systems [30].

Conclusion

The inclusion of film and sugar coatings in tablet formulation is crucial for achieving a highquality appearance, including desirable colour, texture, mouthfeel, and taste masking. The use of aqueous or organic solvents in film and sugar coatings has a significant drawback, which is their potential toxicity. The Tablet in Tablet approach is the most effective solution to address the difficulty outlined above. The Tablet in Tablet technique enables the development of a modified release system for pharmaceuticals, whether they are identical or distinct, belonging to separate categories. This technique allows for the controlled release of drugs at specific absorption sites. Artificial intelligence (AI) plays a crucial role in the development and formulation of cancer tablets. Here's how AI contributes across different stages of the process like Drug Discovery by Identification of Targets and Virtual Screening, Also helps in Formulation Development by Predictive Modeling and Optimization Algorithms.

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