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Review Article

AN EXPERIMENTAL DESIGN IN THE OPTIMIZATION OF VARIOUS TABLET EXCIPIENT FORMULATIONS = A CONCISE REVIEW

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ABSTRACT

The use of an experimental design technique in the development of various pharmaceutical preparations, including tablet preparations, has become the latest trend. Because of their ease of use, tablet formulations are popular among both producers and patients. To increase the usage of tablets in diverse circles and settings, researchers are working to develop a variety of tablet excipients for various functions. Fast dissolving tablets (FDT), effervescent tablets, modified-release tablets, oral mucoadhesive tablets, gastroretentive tablets, and colon targeted tablets are some of the tablet formats that have been developed in addition to traditional tablets. This review will look at how formulation optimization in tablet preparations has been done during the previous ten years using specific literacies. The articles for this review were found using the keywords tablet, excipient, matrices, formulation, and QBD in specialized databases such as Elsevier, Pubmed, and Cambridge. Other options include Springer publications, material from the Internet, and articles published online by The Lancet Respiratory Medicine, Medscape, and Statpearls. The formulation design strategy is based on the experimental design approach carried out on the kind of tablet preparation, which has distinct important quality parameters.

Keywords: Tablet, Excipient, Matrics, Formulation, QBD

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INTRODUCTION

Quality by design (QBD) is a concept of a systematic approach in product development that begins with defining targets and emphasizing product understanding and process control, based on scientific justification and quality risk management. In this concept, the factors that affect the quality of a product are identified early on and optimized simultaneously, systematically, and quickly using a technique called the design of experiment (DoE). This technique was later adopted into the pharmaceutical manufacturing process and termed formulation by design (FbD) [1].

Tablet preparations have very good reception. The ease of handling from the producer and patient side is the advantage of tablet preparations [2]. Therefore, many researchers are developing tablets with various matrices that have their intended use according to the need for safer and more effective therapy. This review summarizes various additives in tableting. It's has been developed according to the type of tablet and the experimental design approach that has been used for development. Ordinarily, additives in different tablet types require properties to support the desired tablet profile. It is necessary to identify critical points in the relevant tablet evaluation. Reviewing the additives in various tablets will be useful information for formulators in preparing the tablet design.

Optimization of various tablet excipients

Conventional tablets

Excipients are utilized in traditional tablets to keep BAF in a compressible mass that can be crushed to release Drug Material into body fluids. As a result, the tablet has earned the moniker of "basic tablet" [3]. The regular tablet is most widely used for rapid-release tablets [3–6]. In addition to their use in medicine, conventional tablets have been produced for herbal preparations, nutraceuticals, and even probiotic bacteria [7–9]. In recent medication development trends, customized drug materials such as nanosuspension, liquid-solid, and solid dispersion drug materials are replacing regular tablets [10–12].

Excipients in traditional tablets are used to contain drug in a compressible mass that can be crushed to release BAF from the excipient into body fluids. As a result, the tablet is known as a simple tablet [3]. For instant release tablets, the standard tablet is most commonly utilized [3–6]. Conventional tablets have been designed for herbal preparations, nutraceuticals, and even probiotic microorganisms in addition to their application in medicine [7–9]. In recent medication development trends, customized BAFs such as nanosuspension, liquid-solid, and solid dispersion drug are replacing regular tablets [10–12]. The survival of bacteria in the excipient, which is referred to as viability in the probiotic tablet, is also regarded as a significant element in formulation optimization [8].

The formulation factors used as independent variables in the optimization of a conventional tablet include fillers, binders, disintegrants, glidants, and lubricants [5, 7]. In addition to formulation factors, process parameters are also involved in the development of conventional tablet preparations, which include the speed and duration of a mixing [7].

Several experimental designs that have been used for the development of conventional tablets include a variety of factorial designs [6, 9], central composite design [8, 11, 15], Box-Behnken design [4, 16, 17], simplex lattice design [7], simplex centroid design [13], optimal mixture design [18].

Fast disintegrating tablet (FDT)

FDT is a preparation with excipients capable of disintegrating in a liquid atmosphere in less than 1 minute. There are two ways to use FDT: dissolved in water and then drunk, and put in the mouth until the excipient disintegrates in the mouth. Tablets with a second use are referred to as orodispersible tablets (ODT). The purpose of FDT is to increase bioavailability in the pre-gastric area, increase the therapeutic effect, and increase drug adherence and acceptance in geriatric and pediatric patients [19–21].

Several quality characteristics in FDT tablets are of particular relevance, in addition to the physical quality parameters that apply to all tablets. Disintegration time with criteria that were faster than normal tablets, tablet wetting time, water absorption ratio, drug release, and flavor were the factors that were focused on while developing FDT excipients [22, 23]. The intended quality metrics, as well as the qualities of additives that affected these parameters, such as disintegrants and sweeteners, might be studied. The disintegrant material employed in FDT might be either a mixture or a super disintegrant [24].

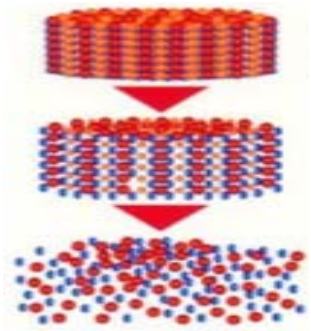

Fig. 1: Basic concept of FDT [19]

Experimental designs that have been used for the development of FDT excipients include factorial designs [22, 23, 25], central composite design [1, 26], Box-Behnken design [27, 28], simplex lattice design [19, 20], simplex centroid design [29].

Effervescent tablets are tablet preparations that release CO_2 when $NaHCO_3$ reacts with organic acids, allowing them to disintegrate and disperse quickly in water. This medication was created for individuals who have trouble swallowing tablets, such as the elderly and children, as well as those who have dysphagia. Preparation was also produced to improve the therapeutic impact [30, 31].

Effervescent preparations, in addition to having physical quality parameters such as tablets in general, must also have a taste that is acceptable to the patient. In addition, foaming time, CO2 content, and pH are also important parameters in the development of effervescent preparations. Thus, formulation attributes that are important to maintaining these quality parameters are sweeteners and the combination of $NaHCO_3$ and organic acids [31]. The experimental design approach to the development of effervescent preparations is still limited. Studies that have been reported have demonstrated the use of factorial and central composite designs [30–32].

Tablet oral mucoadhesive

Bioadhesives, or surfaces that can link to a biological surface, such as the mucosa around the mouth, are produced by excipients in mucoadhesive oral tablets, allowing the preparation to stick in the mouth. The two varieties of this preparation are buccal tablets, which are connected to the mucosa of the cheek area, and sublingual tablets, which are attached to the area under the tongue. The medicine is released into the mouth for rapid absorption through the permeable blood vessels surrounding the oral mucosa, avoiding gastric acid destruction and first-pass effects in the liver. The most prevalent medications produced in this procedure are peptide drugs. Usually, the drugs made in this preparation are peptide drugs. In addition, this preparation can be intended also to provide a local effect on the mouth [33, 34].

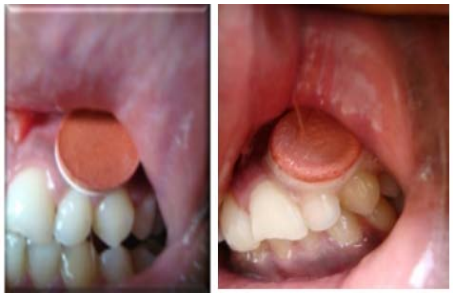

Fig. 2: Mucodhesif oral tablet [33]

The ability of the medicine to diffuse from the preparation and the adhesive strength of the bioadhesive are two critical elements in this preparation. This is related to the drug's requirement for oral mucosal survival and release. As a result, the polymer that aids in the adhesion of this preparation is an important formulation feature to consider. The most often used polymers are hydrophilic [35]. The use of an experimental design technique to produce this preparation is still limited. The usage of factorial and simplex lattice designs has been documented in studies [33–38].

Gastroretentive tablet

Gastroretentive tablets can persist in the stomach. It was intended to increase the bioavailability of the drug in the stomach or maintain a local therapeutic effect on the stomach. There are several types of gastroretentive excipients: excipients that float in gastric fluid with low foaming or density mechanism, bioadhesive excipients, excipients that expand in gastric fluidal, and excipients that sink in gastric fluidal with a high-density mechanism. Several preparations with excipient combinations have also been developed [16, 27, 39–44].

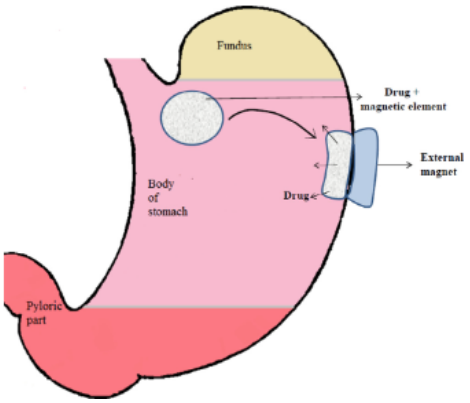

Fig. 2: Gastroretentive tablet [44]

An important quality parameter in gastro retentive preparations is their ability to persist in the stomach according to the kind of excipient and their respective mechanisms, which are usually tested *in vitro* or *in vivo*. In floating excipients, the formulation attribute is an effervescent material or material and process providing a low density. In the bioadhesive excipient, the formulation attribute is an adhesive-forming polymer on the gastric mucosa. In expanding excipients, the attribute of the formulation is that the polymer forms an expanding mass in gastric fluid. In high-density excipients, the formulation attribute is high-density excipients [16, 27, 39, 41, 45].

Experimental designs that have been used for the development of gastroretentive preparations include factorial design, composite design, Box-Behnken design, simple lattice design, and simplex centroid design [16, 27, 46–48].

Modified release tablet

Excipients in modified-release tablets have the ability to hold the drug in such a way that its release can be controlled. This preparation is intended to increase the duration of action of the drug and reduce toxicity. Several excipients have been developed: hydrophilic excipients and osmotic pore excipients [48-50].

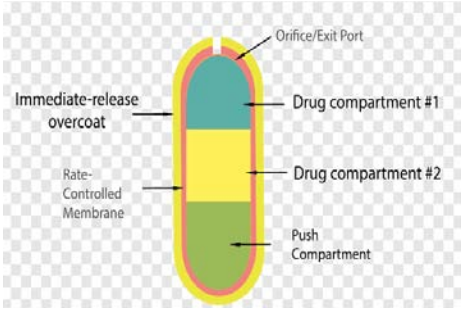

Fig. 4: Modified release tablet system [48]

Table 1: Matrices and experimntal design for floating tablets

No.	Matrices	Experimental design	Refferences
1	Sodium alginat, pectin and sodium bicarbonate	Box-Behnken	Hanif *et al.,* 2017, [16]
2	Hydroxypropyl methylcellulose (HPMC) K15M carboxymethyl tamarind gum (CMTG)	Composite design	Mali *et al.* 2017, [27]
3	HPMC K15M (X1), kappa-Carrageenan (X2) and sodium bicarbonate	Simple lattice design	Kamare *et al.* m, 2021, [46]
4	Hydroxy Propyl Methyl Cellulose K4M, ethyl cellulose (4cps) and sodiumbicarbonate	Full actorial design	Maddiboyina *et al.* 2020, [47]
5	ethocel K100LV, Methocel K15M and Carbopol 934	Simplex centroid design	Raza *et al.*, 2017, [48]

The drug release profile is the typical quality parameter of this preparation because the objective of this excipient is to modify drug release. As a result, the elements that operate to contain the medication material are the formulation features that need to be adjusted. The formulation attribute for hydrophilic excipients is hydrophilic polymeric polymers. The formulation attribute for osmotic pore excipients is in situ pore-forming polymeric polymers [51–53]. The factorial design, central composite design, Box-Behnken design, and simplex centroid design have all been used in the creation of modified loose dosage forms [54–58].

Colon targeted tablets

Tablets that are colon-targeted do not break down in the digestive tract until they reach the small intestine. This formulation was designed to have a local therapeutic impact, similar to how antibiotics are used to treat infections of the large intestine. These formulations can be used to boost protein and peptide drug absorption [59, 60].

The ability of the dosage form to endure degradation in the gastrointestinal tract, the drug release profile in the large intestine, and the percentage of drug entrapment are all quality characteristics to consider in this preparation. Coating materials and hydrophilic polymer excipients are two formulation properties that must be maintained [61, 62]. The experimental designs that have been used, such as design factorial and central composite design [61, 62], are still limited.

CONCLUSION

The experimental design approach has become a new trend in the development of various tablet excipients. The various experimental designs, the factorial design is the most chosen because of its flexibility. In general, the development of effervescent, oral mucoadhesive, and colon targeted excipients, research with an experimental design approach is still limited to a small number of experiment design variations.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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