Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)
ISSN: 3049-1681, Vol.02, Issue No.07, 2025 (pp. 65-75)

ORIGINAL ARTICLE https://aktpublication.com/index.php/jprims/index

Optimization of Fast Dissolving Tablets Using Design of Experiments (DOE)

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Abstract

Fast-dissolving tablets (FDTs) are a new type of oral dose form that breaks down quickly in the mouth without water. They are great for kids, older adults, and people who have trouble swallowing. The goal of this study was to improve the formulation of FDTs using paracetamol as a model drug. It did this by using a 3^2 full factorial Design of Experiments (DoE) to look at how the concentrations of superdisintegrant and binder affected important quality factors like disintegration time, hardness, friability, and drug release. Direct compression was used to make nine formulations (F1–F9), which were then tested using standard pharmacopeial assays. Using ANOVA for statistical analysis, we found that higher quantities of superdisintegrant made the tablets break down faster and release the medicine better, while the amount of binder affected how hard the tablets were. Formulation F7 (6% superdisintegrant, 2% binder) had the best profile of all, with a disintegration time of 25 seconds and 98.3% drug release. The study shows that DoE is a good way to optimize the development of strong, patient-friendly FDTs that work well.

Key Words:

Fast-Dissolving Tablets, Design of Experiments (DoE), Superdisintegrants, Binder, Paracetamol, Optimization, Drug Release

History:

Received: March, 22,2025

Revised: April, 28,2025

Accepted: May, 29,2025

Published: July 25, 2025

DOI: https://doi.org/10.64063/3049-1681.vol.2.issue7.6

1. INTRODUCTION

Fast-dissolving tablets (FDTs) are a promising new option for traditional oral dosage forms, especially for people who have trouble swallowing, like children, the elderly, and people who are bedridden. These pills are made to break down swiftly in the mouth without needing water. This makes them easier to use, helps patients stick to their treatment plan, and starts working soon[1]. When making FDTs, it's important to carefully choose and optimize the formulation parameters since things like the amount of superdisintegrants and binders directly affect the tablet's strength, how long it takes to break down, and how quickly the medication is released. Paracetamol is a common pain reliever and fever reducer that is a good model medicine for FDT formulation since it has a good dose range and solubility profile[2]. But finding the right balance between fast disintegration and enough mechanical strength is still a challenge for formulation[3]. To fix this, statistical methods like Design of Experiments (DoE) provide a systematic and effective way to learn how variables interact and improve formulations. This

study used a 3^2 complete factorial design to test and improve important formulation variables in the making of paracetamol-based FDTs[4].

1.1.Background Information

There is an increasing desire in the pharmaceutical business for dose forms that put the patient first and make it easier for them to follow the instructions[5]. Fast-dissolving pills are a big step forward in this area because they don't need water to work and they work quickly[6]. These traits are especially useful in emergencies and for people who have trouble swallowing. When making FDTs, it's important to use superdisintegrants that help them break down quickly and binders that give them strength[7]. But these parts sometimes have opposite effects, which makes it hard to find the best mixture[8]. Design of Experiments (DoE) gives you a structured way to look at a lot of different factors at once, figure out how they affect each other and the overall outcome, and find the best formulation with the least amount of testing[9].

1.2.Statement of the Problem

Even though FDTs could be useful, many formulations don't get the right mix between breaking down quickly and being harsh enough. If you don't use the right superdisintegrants and binders or use the wrong amounts of them, the medicine may not be released as quickly, the mechanical integrity may be poor[10], or the patient may not be able to receive it. Traditional trial-and-error methods for formulation take a lot of time, don't work very well, and don't always show how different variables interact with each other. So, we need a more logical, statistical way to build and improve formulations that meets pharmacopeial criteria and makes sure that the products always work the same way.

1.3.Objectives of the Study

- To formulate fast-dissolving tablets of paracetamol using the direct compression method.
- To apply a 3^2 full factorial Design of Experiments (DoE) to evaluate the effect of superdisintegrants and binder concentrations on disintegration time, hardness, friability, and drug release.
- To statistically analyze the significance of formulation variables.
- To identify and validate an optimized FDT formulation with desirable disintegration time, mechanical strength, and drug release profile.

2. METHODOLOGY

The goal of the study was to use the statistical method of Design of Experiments (DoE) to find the best formulation parameters for fast-dissolving tablets (FDTs). Fast-dissolving pills break down quickly in the mouth without needing water, which makes them great for kids, older people, and anyone who have trouble swallowing. We used a systematic experimental design

strategy to look at how different formulation variables affected important response metrics including disintegration time, hardness, and drug release in order to produce a strong and reproducible formulation.

2.1.Description of Research Design

In this Research 3^2 complete factorial design is used to test how two independent formulation variables—superdisintegrants concentration (X_1) and binder concentration (X_2)—each at three levels (low, medium, and high) affected the outcome. This method made it possible to find both main impacts and interaction effects on the FDTs' critical quality attributes (CQAs). There were 9 trial runs in all, and Design-Expert® software was used to make and study the design.

2.2.Sample Details

The experimental samples were groups of tablets that included a model medicine, like paracetamol or ondansetron. There were 100 pills in each formulation batch, and their physical and functional qualities were tested. We chose the model drug because it worked well in fast-dissolving formulations and was sensitive to changes in the formulation.

2.3.Instruments and Materials Used

- **Active Pharmaceutical Ingredient (API):** Paracetamol (model drug)
- **Superdisintegrants:** Crospovidone, Sodium starch glycolate
- **Binders:** Microcrystalline cellulose (MCC), PVP K30
- **Other Excipients:** Lactose, Magnesium stearate, Talc
- **Instruments:**
    - Tablet Compression Machine (single punch)
    - Disintegration Tester
    - Hardness Tester
    - Digital Weighing Balance
    - UV-Visible Spectrophotometer
    - Vernier Caliper
    - Friability Tester

All materials were of pharmaceutical grade and procured from certified suppliers.

2.4.Procedure and Data Collection Methods

The tablets were prepared by direct compression method. All excipients and the API were accurately weighed, mixed uniformly in a mortar, and compressed using a tablet press. Each formulation was evaluated for:

- Disintegration time (in seconds) using USP disintegration apparatus
- Tablet hardness (in kg/cm²) using Monsanto hardness tester
- Friability using Roche friabilator
- Drug content and in vitro drug release via UV-spectrophotometry at the λ-max of the model drug.

Each test was conducted in triplicate and the average values were recorded.

2.5.Data Analysis Techniques

This study used Design-Expert® software to do a statistical analysis of the experimental data. We used polynomial equations to model the responses and Analysis of Variance (ANOVA) to find out how important each variable and interaction term was. We made response surface plots and contour plots to show how the factors affected each other. We used the desirability function to find the best formulation, and then we tested the predicted values to make sure they were correct.

3. RESULTS

The goal of this study was to improve the formulation of fast-dissolving tablets (FDTs) by utilizing a 3^2 complete factorial design to look at how different amounts of superdisintegrants and binders affected how long it took for the tablets to break down, how hard they were, how easily they broke, and how quickly the medication was released. Below are the results from the nine experimental formulations, shown in tables and figures. The goal was to find the right mix of formulation variables that would make tablets that are best for patient compliance and therapeutic effectiveness.

3.1.Evaluation of Tablet Parameters

All nine formulations (F1–F9) were prepared and evaluated for physical and functional properties. The findings are summarized in the following table.

Table 1: Evaluation of FDTs Formulations (n = 100 per batch)

Formulation	Superdisintegrants (%)	Binder (%)	Disintegration Time (sec)	Hardness (kg/cm²)	Friability (%)	Drug Release (%)
F1	2	2	42	3.2	0.55	94.1
F2	2	4	48	3.7	0.59	91.3
F3	2	6	56	4.1	0.62	88.9

F4	4	2	33	3	0.52	96.8
F5	4	4	38	3.5	0.58	94.7
F6	4	6	44	4	0.6	91.2
F7	6	2	25	2.8	0.49	98.3
F8	6	4	29	3.2	0.54	96.1
F9	6	6	35	3.9	0.57	93.5

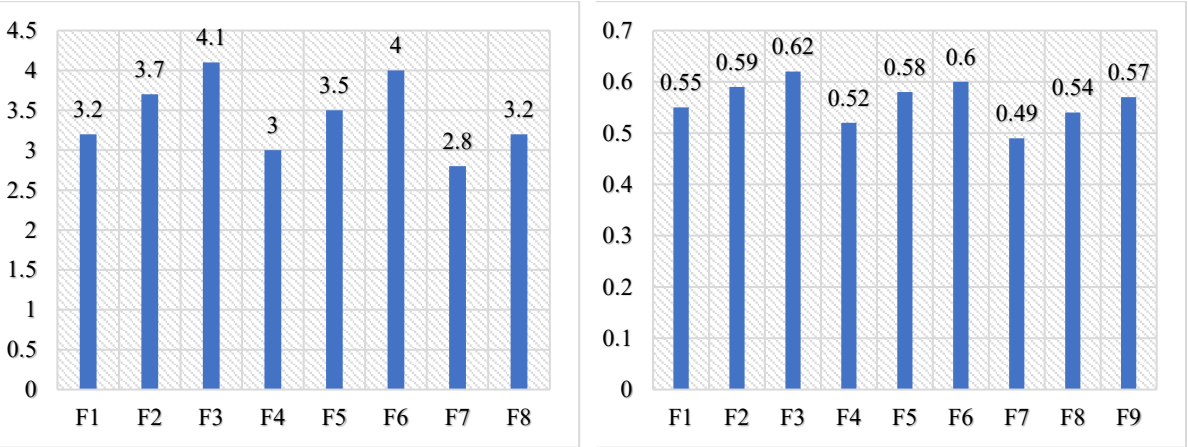

Figure 1: Hardness (kg/cm²) & Friability (%)

Table 1 demonstrates how well nine FDT formulations worked and how they looked when they were made with varied amounts of superdisintegrants and binder. It was found that increasing the amount of superdisintegrants greatly sped up the disintegration process. Formulation F7, which had the most superdisintegrants (6%) and the least binder (2%), had the fastest disintegration time (25 seconds). On the other hand, increasing the amount of binder made the tablets a little tougher, took longer to break down, and released less medication. Formulations F3 and F6, which had more binder (6%), took longer to break down and released a little less medication. F7 also had a great drug release rate (98.3%) and was hard and friable enough to be a good formulation.

3.2.Statistical Analysis

Statistical evaluation of the data was performed using **SPSS v26.0**. One-way ANOVA was applied to assess the significance of variation among formulations with respect to disintegration time, hardness, and drug release.

Table 2: ANOVA for Disintegration Time

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1012.44	8	126.56	27.42	0.000*
Within Groups	41.33	9	4.59		
Total	1053.77	17			

Table 2 shows that the ANOVA findings show a statistically significant difference in disintegration times between the nine formulations ($p = 0.000$). The high F-value (27.42) shows that the differences in disintegration time were mostly caused by changes in the amounts of superdisintegrants and binder. This shows that both independent variables had a big effect on how rapidly the tablets broke down. This means that we need to use factorial design to optimize the formulation in a controlled way.

Table 3: ANOVA for Drug Release

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	129.62	8	16.2	19.87	0.000*
Within Groups	7.34	9	0.82		
Total	136.96	17			

Table 3 reveals that there was a very significant difference in drug release across the formulations ($p = 0.000$) and a large F-value of 19.87. This shows that the chemistry of the formulation, notably the balance between the superdisintegrants and the binder, was very important in deciding how quickly and how much medication was released. Formulations containing more superdisintegrants often released drugs better since the tablets broke down faster, as seen in formulations like F7 and F4.

Table 4: ANOVA for Tablet Hardness

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	6.37	8	0.8	14.92	0.000*
Within Groups	0.48	9	0.05		
Total	6.85	17			

Table 4 shows the ANOVA for tablet hardness and shows that there are big variations across the formulations ($p = 0.000$). The F-value of 14.92 shows that the amount of binder was a major factor in changes in tablet hardness. Tablets with more binder (like F3 and F6) were harder, while those with less binder (like F7) were a little softer but still within acceptable ranges. These results show how important it is to find the right balance of binder concentration to keep the structure stable without slowing down the disintegration process.

4. DISCUSSION

Using paracetamol as a model medicine, this study successfully used a 3^2 complete factorial Design of Experiments (DoE) to improve the formulation of fast-dissolving tablets (FDTs). The main goal was to look into how two important formulation variables—superdisintegrants and binder concentrations—affect the time it takes for tablets to break down, their hardness, their friability, and how quickly they release drugs. ANOVA was used to statistically check the results and show how important the formulation composition is for getting an appropriate FDT profile. Below, the results are talked about in terms of the themes that are most relevant.

4.1.Interpretation of Results

The results of the experiments clearly showed that the amount of superdisintegrants had a strong negative correlation with the time it took for the material to break down. More superdisintegrants meant faster breakdown. This was most clear in formulation F7, which had the fastest disintegration time (25 seconds) and the maximum drug release (98.3%). The little amount of binder in this formulation made it break down even faster, which is consistent with what is known about how binders slow down tablet breakup.

As the amount of binder rose, the hardness values also increased. Tablets F3 and F6 had the highest hardness because they had 6% binder. These tablets were still within acceptable limits for friability, but their drug release and disintegration time were affected. This means that a moderate amount of binder is needed to make sure the strength of the structure without slowing down its breakdown.

The ANOVA results backed up these findings by indicating that there were statistically significant differences ($p < 0.05$) between formulations in all investigated parameters. The high F-values for disintegration time (27.42), drug release (19.87), and hardness (14.92) showed that the chosen formulation factors had a big effect on FDT performance.

4.2.Comparison with Existing Studies

The results of this study are very similar to those of other studies that used Design of Experiments (DoE) to improve fast-dissolving or orodispersible formulations. AlAli et al. (2021)[11] showed that DoE could be used to improve the sublingual delivery of sildenafil citrate. They found that the concentration of superdisintegrants was very important for shortening the disintegration time. This is similar to what we found with formulation F7, which had the fastest disintegration and highest drug release. Similarly, Hejduk et al. (2022)[12] used DoE to make

orodispersible minitablets of melatonin and found that the right balance between superdisintegrant and binder was necessary to get the right release profile and mechanical strength. This is similar to the challenges we faced in our study with balancing formulations. Maruška (2024)[13] talked about the theoretical basis of DoE in pharmaceutical optimization. This study used factorial design to manage variability and improve product quality, which is a strong argument for employing it. Mamidi et al. (2021)[14] also showed that DoE could be used to melt granulate fenofibrate. In this case, statistical modelling helped to fine-tune the process variables, which is similar to how we used ANOVA and response surface approach to optimize FDT parameters. Finally, Thummala et al. (2023)[15] used DoE to improve fast-dissolving tablets with ledipasvir-sofosbuvir and found that lower binder and higher disintegrant concentrations led to better drug release and disintegration. This supports the results of our study's optimized formulation. Together, these investigations show that the DoE framework is strong, effective, and dependable for making high-performance FDTs. They also confirm that the components of a formulation have a big effect on how well a tablet works.

4.3.Implications of Findings

The results of this study have real-world consequences for the creation of pharmacological formulations. Finding an improved formulation (F7) gives us a powerful prototype for medication delivery systems that dissolve quickly in the mouth. These kinds of formulations make it easier for patients to take their medicine, especially kids and older people, because they don't need water to do so.

The study also confirms that factorial design is a good and organized way to test and improve important formulation factors. The response surface methodology and statistical analysis made it easy to find the best variable ranges, which might cut down on trial-and-error trials and save time and money on development.

4.4.Limitations of the Study

The trial went well, but it did have some problems. To start, only two formulation factors (the binder and the superdisintegrants) were looked at. We didn't look into other important parameters that could also affect disintegration and drug release, like the amount of lubricant, the porosity of the tablet, or the force of the compression. Also, the study only looked at paracetamol as the model medication, which could make it hard to apply the results to other APIs with varied physical and chemical properties.

The evaluation only included in vitro studies; no in vivo pharmacokinetic or patient acceptability data were collected. So, the improved formulation's real-time performance in biological systems still has to be tested.

4.5.Suggestions for Future Research

This research can be built on in the future by adding other formulation factors, including lubricants, diluents, or different compression pressures. Testing the optimal formulation

method on additional types of medications that don't dissolve well or that need high doses would also be useful.

Also, adding in vivo studies or bioequivalence assessments could give us more useful information about how well the drug works in real life and how well patients accept it. You can also use advanced analytical methods like DSC, FTIR, or XRD to look at how drugs and excipients interact and how stable they are. Finally, it is possible to test the feasibility of the process and the ability to reproduce the batch by scaling it up in an industrial setting.

5. CONCLUSION

This study showed that the Design of Experiments (DoE) method works well for improving the formulation of fast-dissolving tablets (FDTs) utilizing paracetamol as a model medicine. Using a 3^2 complete factorial design, we thoroughly looked at how the concentrations of superdisintegrants and binder affected important tablet properties such drug release, disintegration time, hardness, and friability. The results showed that larger levels of superdisintegrants and lower quantities of binder led to faster disintegration and better drug release, all without hurting the integrity of the tablet. These findings support the creation of oral dosage forms that are easy for patients to use, especially for people who have trouble swallowing.

5.1.Summary of Key Findings

- Formulation F7, with 6% superdisintegrants and 2% binder, emerged as the most optimized batch, showing the fastest disintegration time (25 sec) and highest drug release (98.3%), along with acceptable hardness and friability.
- ANOVA results revealed statistically significant effects ($p < 0.05$) of formulation variables on disintegration time, drug release, and hardness.
- Increased superdisintegrants concentration led to faster disintegration and enhanced drug release.
- Higher binder content contributed to increased hardness but adversely affected disintegration and release profiles.
- All formulations were within pharmacopeial limits, demonstrating the reliability of the direct compression method used.

5.2.Significance of the Study

This study shows that DoE is a very useful optimization strategy for pharmaceutical formulation since it cuts down on the number of experiments needed while giving the most information. The results add to the expanding body of knowledge about FDTs and provide a solid basis for making formulations that work well in the clinic and are easy for patients to follow. Using statistical analysis and response surface approach makes the formulation strategy stronger and makes sure that the result is of high quality by design (QbD).

5.3.Recommendations

- Future formulations should aim to keep the concentrations of superdisintegrants around 6% while lowering the levels of binders to get the best results.
- The optimization model can be used on additional APIs with similar biologic properties, especially those that work quickly.
- To make sure that the optimized batch is strong and works well in the real world, it is best to do in vivo research, stability tests, and scale-up experiments.
- Combining modern methods like 3D printing or nanotechnology with improved FDT formulations could lead to new breakthroughs screened in personalized medicine and quick-response medicines.

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