*Original Article*

# Design, Formulation and Evaluation of Pravastatin Fast Dissolving Tablets.

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## ABSTRACT

**Objective:** The main objective of present research investigation is to formulate the Pravastatin Fast Dissolving tablets. Pravastatin, a newer antihyperlipidemic agent, belongs BCS class-III agent and used to treat hypercholesterolemia and to reduce the risk of Cardiovascular disease. **Methods:** The Fast Dissolving tablets of Pravastatin were prepared employing various concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Superdisintegrants by Direct Compression technique using $3^2$ factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, $X_1$ and $X_2$ respectively whereas, wetting time, Disintegration time, $t_{50\%}$, $t_{90\%}$ were selected as dependent variables. **Results and Discussion:** Totally nine formulations were designed and are evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be with in the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, $t_{50\%}$, $t_{90\%}$. Validity of developed polynomial equations were verified by designing 2 check point formulations ($C_1$, $C_2$). According to SUPAC guidelines the formulation ($F_1$) containing combination of 8% Crospovidone and 8% Croscarmellose, is the most similar formulation (similarity factor $f_2$= 89.724, dissimilarity factor $f_1$= 1.307 & No significant difference, t= 0.0465) to marketed product (PRAVACHOL-40). **Conclusion:** The selected formulation ($F_5$) follows First order, Higuchi's kinetics, mechanism of drug release was found to be Non-Fickian Diffusion Super Case-II Transport (n= 1.875).

**Key words:** Pravastatin, $3^2$ Factorial design, Super disintegrants, Crospovidone, Croscarmellose sodium, Wetting time, Disintegration time, Non-Fickian diffusion.

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DOI : 10.5530/phm.2018.1.4

## INTRODUCTION

Researchers throughout the world are focusing intensively on the methods for the development of new drug delivery systems to enhance patient's compliance. Fast dissolving tablets become an emerging trend in the pharmaceutical industry. Fast dissolving tablets are ideal for all types of people, including for people who have swallowing difficulties, pediatric, geriatric, and bedridden patients. Fast dissolving tablets are also known as orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. Many drugs have the potentials to be made into orodispersible tablets.[1]

The speed of solubility of drug affects the rate of absorption of the drug. The faster the drug dissolve into solution, quicker the absorption and onset of clinical effect. They should readily dissolve or disintegrate in the saliva generally within<60 seconds. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The significance of oral disintegrating dosage forms is progressively being recognized in both, industry and academics. The small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. Orally disintegrating tablets (ODT) are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as, mechanical strength of tablet, taste and mouth feel, swallowability, drug dissolution in saliva, bioavailability and stability. Various processes employed in formulating ODTs include Freeze-Drying or Lyophilization, cotton candy process, molding, spray drying, mass extrusion and compaction (wet granulation, dry granulation, and direct compression).

In the present study, the direct compression method was adopted to manufacture the ODT tablets, since it was very simple and do not require any sophisticated equipment's. The direct compression represents the simplest and most cost-effective tablet manufacturing technique.[2]

ODT by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.

## Drug Profile and Rationality for Experimental Design

Pravastatin is a HMG CoA inhibitor used as antihyperlipidemic agent, belongs to BCS Clas-III drug. It has High Aqueous Solubility (300 mg/ml) and low permeability characteristics. It shows Low absolute oral Bioavailability (17%). It has a short biological half-life (1-1.5 h) and undergoes extensive first-pass metabolism (due to decreased permeability).[3-4]

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The

technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms.[5-8]

Hence an attempt is made in this research work to formulate Fast Dissolving Tablets of Pravastatin using Crospovidone and Croscarmellose sodium. Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The Fast Dissolving tablets formulation by direct compression method is most acceptable in large scale production.

A $3^2$ full factorial design was employed to systematically study the drug release profile. A $3^2$ full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of Crospovidone and Croscarmellose on the dependent variables, i.e. Disintegration time, Wetting time, $t_{50\%}$, $t_{90\%}$, (Time taken to release 50%, 90% respectively)

## MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Pravastatin was a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. Avicel pH101, Crospovidone, Croscarmellose sodium, were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as Magnesium Stearate, talc was procured from S.D. Fine Chem. Ltd., Mumbai.

## Formulation Development of Pravastatin Fast Dissolving Tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses.[9,10]

A selected three level, two factor experimental design ($3^2$ factorial design) describe the proportion in which the independent variables Crospovidone and Croscarmellose sodium were used in formulation of Pravastatin Fast Dissolving Tablets. The time required for 50% ($t_{50\%}$), 90% ($t_{90\%}$) drug dissolution, Disintegration Time and Wetting Time were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{50\%}$, $t_{90\%}$, Disintegration Time and Wetting Time (step-wise backward Linear Regression Analysis). The three levels of factor $X_1$ (Crospovidone) at a concentration of 8%, 6%, 4%. Three levels of factor $X_2$ (Croscarmellose sodium) at a concentration of 8%, 6%, 4%. (% with respect to average weight of Tablet, i.e 200 mg) was taken as the rationale for the design of the Pravastatin Fast Dissolving tablet formulation. Totally nine Pravastatin Fast Dissolving tablet formulations were prepared employing selected combinations of the two factors i.e, $X_1$, $X_2$ as per $3^2$ Factorial and evaluated to find out the significance of combined effects of $X_1$, $X_2$ to select the best combination and the concentration required to achieve the desired Fast release/ Dissolution of drug (by providing large Surface area and Improved Solubility) from the dosage form.

## Preparation of Pravastatin Fast Dissolving Tablets

Pravastatin Tablets were prepared by direct compression method. The composition of each tablet is shown in Table 2. The drug, diluents, Super disintegrates were passed through sieve #40. All the above ingredients were properly mixed together (in a poly-bag). Talc and Magnesium

stearate were passed through mesh #80, mixed and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets on 8 station rotary punch tableting machine (minipress) using 8 mm circular punches and same hardness was used for the required number tablets. Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

## Experimental Design

Experimental design utilized in present investigation for the optimization of Superdisintegrant concentration such as, concentration of Crospovidone was taken as $X_1$ and concentration of Croscarmellose sodium was taken as $X_2$. Experimental design was given in the Table 1. Three levels for the Concentration of Crospovidone were selected and coded as -1= 4%, 0=6%, +1=8%. Three levels for the Concentration of Croscarmellose sodium were selected and coded as -1= 4%, 0=6%, +1=8%. Formulae for all the experimental batches were given in Table 2.[5-11]

Evaluation of pravastatin fast dissolving tablets:

## Hardness

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 Kg/cm$^2$ is considered adequate for mechanical stability.[12]

## Friability

The friability of the tablets was measured in a Roche friabilator (Campbell Electronics, Mumbai). 20 Tablets were taken, Weighed and Initial

### Table 1: Experimental Design Layout

| Formulation Code | $X_1$ | $X_2$ |
|---|---|---|
| $F_1$ | 1 | 1 |
| $F_2$ | 1 | 0 |
| $F_3$ | 1 | -1 |
| $F_4$ | 0 | 1 |
| $F_5$ | 0 | 0 |
| $F_6$ | 0 | -1 |
| $F_7$ | -1 | 1 |
| $F_8$ | -1 | 0 |
| $F_9$ | -1 | -1 |
| $C_1$ | -0.5 | -0.5 |
| $C_2$ | +0.5 | +0.5 |

### Table 2: Formulae for the Preparation of Pravastatin Fast Dissolving Tablets as Per Experimental Design

| Name of Ingredients | Quantity of Ingredients per each Tablet (mg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ |
| Pravastatin | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| MCC pH-101 | 120 | 124 | 128 | 124 | 128 | 132 | 128 | 132 | 136 |
| Crospovidone | 16 | 16 | 16 | 12 | 12 | 12 | 8 | 8 | 8 |
| Croscarmellose sodium | 16 | 12 | 8 | 16 | 12 | 8 | 16 | 12 | 8 |
| Magnesium Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Total Weight | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

weight was noted ($W_0$) are dedusted in a drum for a fixed time (100 revolutions, in a Roche Friabilator) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.[12]

**Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100**

## Content Uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or not more than 17.5% (100±7.5%) of the labeled drug content can be considered as the test was passed.[13]

## Assay

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The powder equivalent to 100 mg Pravastatin was weighed and dissolved in 10 ml of Distilled water in volumetric flask, the volume was adjusted to 100 ml with Phosphate buffer pH 6.8and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content in was determined spectrophotometrically at 239 nm.[3-14]

## Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.[12]

## Wetting time

To measure Wetting time of the Tablet, a piece of Tissue paper folded twice was placed in a small petri dish (Internal Diameter is= 6.5 cm) containing 5 ml of Distilled water. A Tablet placed on the paper, and the time for complete wetting of the tablet was measured in seconds.[15-17]

## *In-vitro* Dissolution Study

The *in-vitro* dissolution study for the Pravastatin Fast Dissolving tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of Phosphate buffer pH 6.8 as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 239 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).[3-14]

## Disintegration test

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva, however Quantity of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh screens was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.[15]

## Kinetic modeling of drug release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, and Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release.[18-21]

## RESULTS AND DISCUSSION

Fast Dissolving tablets of Pravastatin were prepared and optimized by $3^2$ factorial design in order to select the best combination of different Superdisintegrants, Crospovidone, Croscarmellose sodium and also to achieve the desired rapid release of drug from the dosage form (by Disintegrating quickly). The two factorial parameters involved in the development of formulations are, quantity of Crospovidone & Croscarmellose sodium as independent variables ($X_1$, $X_2$), and *in vitro* dissolution parameters such as $t_{50\%}$, $t_{90\%}$, Wetting time and Disintegrating Time as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 40 mg of Pravastatin were prepared as a Fast Dissolving tablet dosage form by Direct Compression technique as per the formulae given in Table 2. All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods and results are given in Table 3. The hardness of tablets was in the range of 4.01±0.075-4.60±0.225 Kg/cm². Weight loss in the friability test was not more than 0.70%. Drug content of prepared tablets was within acceptance range only. The Wetting Time of tablets was in the range of 31.05±0.75-62.95±0.85 sec. The Disintegration Time of tablets was in the range of 21.53±0.65-41.88±0.8 sec. Results for all Post-compression parameters were tabulated or shown in Table 3. *In-vitro* Dissolution studies were performed for prepared tablets using Phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. The *in-vitro* dissolution profiles of tablets are shown in Figure 1-4. (Kinetic Plots), Wetting Time Chart, Disintegration Time charts were shown in Figure 5,6. The dissolution parameters are given in Table 4. Cumulative % Drug release of Factorial Design Formulations $F_1$-$F_9$ at 30 mins were found to be in the range of **91.825-99.14 %**. From the result, it reveals that the release rate was higher for formulations containing High level of Crospovidone/Croscarmellose sodium compared with other Formulations containing Lower level, due to High concentration of Superdisintegrant in combination, shows various disintegration mechanism such as wicking and swelling etc more compared with lower concentration and alone, drug may release rapidly and shows improved bioavailability. Excess of Superdisintegrant also prone to Friable. Therefore, required release of drug can be obtained by manipulating the composition of Crospovidone and Croscarmellose sodium.

Variation was observed in the Wetting time, Disintegrating time, $t_{50\%}$ and $t_{90\%}$ due to formulation variables. Formulation $F_1$ containing 16 mg of Crospovidone, 16 mg of Croscarmellose sodium showed promising dissolution parameter (**Wetting time** = 31.05±0.75 sec, **Disintegrating time** = 21.53±0.65 sec, $t_{50\%}$ = **6.573 min**, $t_{90\%}$ = **21.843 min**). The difference in burst effect of the initial time is a result of the difference in the Concentration of Superdisintegrants mixtures. This reveals that increased concentration of superdisintegrants resulted in a corresponding decrease in the Wetting Time, which might be due to the result of wicking and other possible disintegrating mechanisms. Disintegration time is directly proportional to wetting time. The *in -vitro* dissolution data of Pravastatin Fast Dissolving formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4. It was observed from the above that dissolution of all the tablets followed First order kinetics with co-efficient of determination (R²) values in the range of **0.957-**
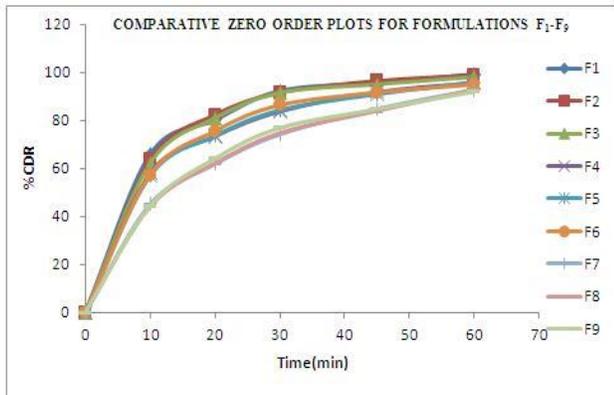
**Figure 1:** Comparative Zero Order Plots.
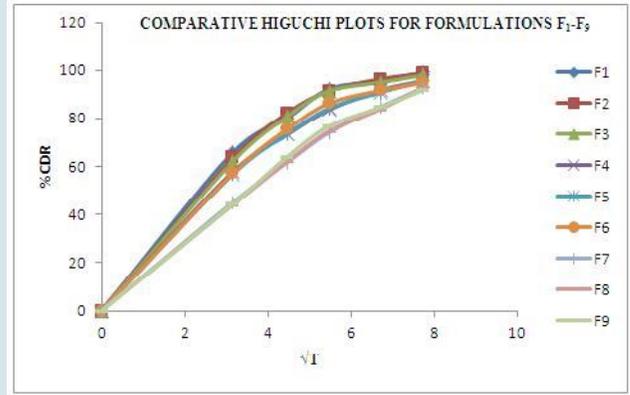


**Figure 3:** Comparative Higuchi Plots.
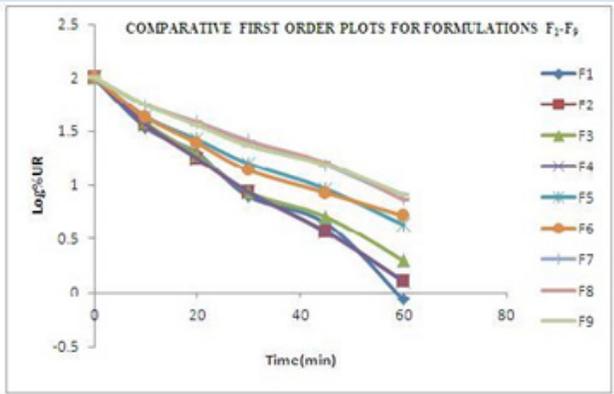


**Figure 2:** Comparative First Order Plots.
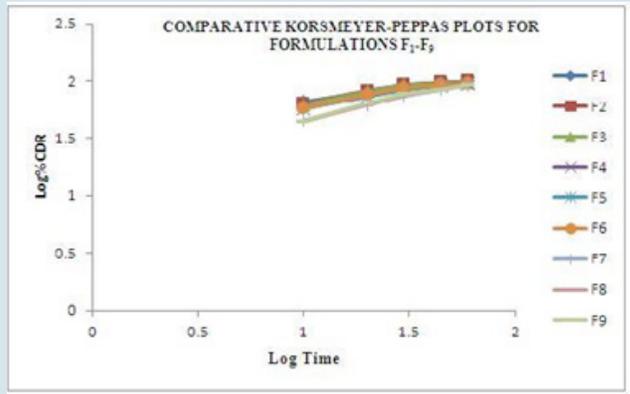


**Figure 4:** Comparative Korsmeyer Peppas Plots.

**Table 3: Post-Compression Parameters for the Formulations**

| Formulation Code | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | % Weight Variation | Drug Content (%) | Wetting Time( sec) | Disintegration Time (sec) |
|---|---|---|---|---|---|---|---|
| F1 | 4.6±0.225 | 3.66±0.225 | 0.67±0.03 | Pass | 98.045±0.45 | 31.05±0.75 | 21.53±0.65 |
| F2 | 4.25±0.17 | 3.65±0.275 | 0.685±0.025 | Pass | 98.26±0.33 | 33.94±0.8 | 23.11±0.7 |
| F3 | 4.20±0.185 | 3.725±0.187 | 0.675±0.03 | Pass | 97.39±0.24 | 34.57±0.9 | 24.13±0.8 |
| F4 | 4.35±0.19 | 3.61±0.082 | 0.665±0.025 | Pass | 98.08±0.515 | 34.03±0.7 | 23.72±0.7 |
| F5 | 4.01±0.135 | 3.60±0.132 | 0.68±0.02 | Pass | 98.285±0.395 | 36.93±0.75 | 25.33±0.75 |
| F6 | 3.95±0.15 | 3.675±0.044 | 0.67±0.025 | Pass | 97.42±0.30 | 55.26±0.85 | 41.36±0.85 |
| F7 | 4.41±0.115 | 3.61±0.079 | 0.635±0.025 | Pass | 99.135±0.595 | 55.29±0.7 | 38.48±0.65 |
| F8 | 4.05±0.06 | 3.60±0.13 | 0.65±0.02 | Pass | 99.345±0.475 | 60.42±0.75 | 41.04±0.75 |
| F9 | 4.01±0.075 | 3.675±0.04 | 0.64±0.025 | Pass | 98.48±0.38 | 62.95±0.85 | 41.88±0.8 |

**0.994**. The values of r of factorial formulations for Higuchi's equation was found to be in the range of **0.868-0.993**, which shows that the dissolution data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from **1.243-1.875** that shows Non-Fickian diffusion mechanism. Polynomial equations were derived for Wetting time, disintegrating time, $t_{50\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis using **PCP Disso** software and Response surface plots were constructed using **SIGMAPLOT V13** software. The Response surface plots were shown in Fig.7-10 for Wetting time, disintegrating time, $t_{50\%}$ and $t_{90\%}$ using $X_1$ and $X_2$ on both the axes respectively. The dissolution data (Kinetic parameters) of factorial for-
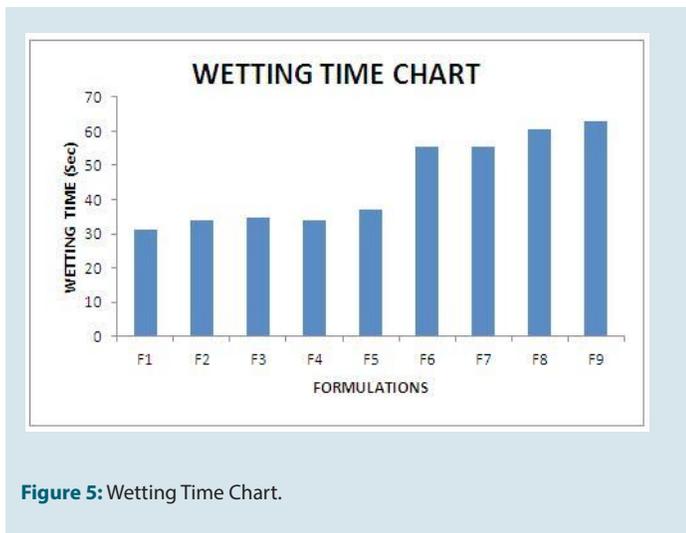
**Figure 5:** Wetting Time Chart.
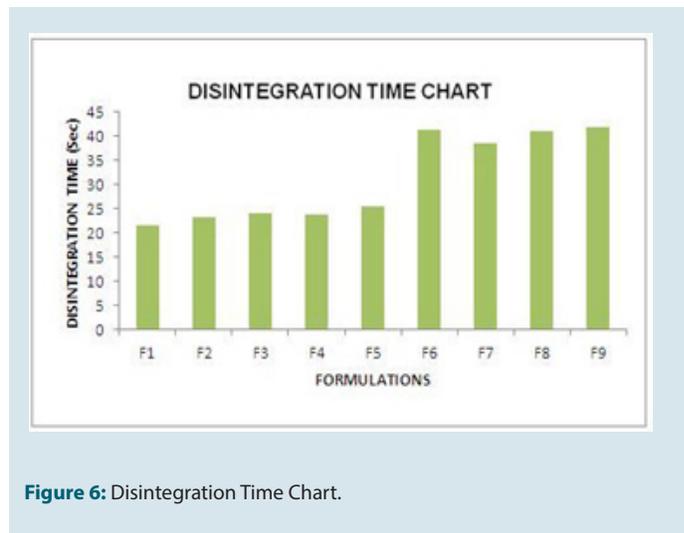


**Figure 6:** Disintegration Time Chart.

**Table 4: Regression Analysis Data of 32 Factorial Design Formulations of Pravastatin Fast Dissolving Tablets**

| Formulation Code | Kinetic Parameters | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Zero Order | | | First Order | | | Higuchi | | | Korsmeyer-Peppas | | |
| | a | b | r | a | b | r | a | b | r | a | b | r |
| F1 | 47.103 | 1.199 | 0.677 | 1.718 | 0.046 | 0.957 | 23.202 | 12.381 | 0.868 | 1.875 | 0.075 | 0.929 |
| F2 | 34.507 | 1.365 | 0.811 | 1.924 | 0.032 | 0.994 | 12.802 | 12.892 | 0.951 | 1.575 | 0.247 | 0.968 |
| F3 | 33.847 | 1.360 | 0.814 | 1.908 | 0.029 | 0.984 | 12.360 | 12.815 | 0.953 | 1.559 | 0.255 | 0.965 |
| F4 | 34.507 | 1.365 | 0.811 | 1.924 | 0.032 | 0.994 | 12.802 | 12.892 | 0.951 | 1.575 | 0.247 | 0.968 |
| F5 | 29.643 | 1.353 | 0.849 | 1.918 | 0.023 | 0.986 | 9.633 | 12.451 | 0.970 | 1.476 | 0.292 | 0.988 |
| F6 | 30.716 | 1.340 | 0.835 | 1.914 | 0.024 | 0.984 | 10.369 | 12.447 | 0.963 | 1.492 | 0.284 | 0.974 |
| F7 | 21.824 | 1.377 | 0.910 | 1.956 | 0.018 | 0.994 | 4.082 | 12.106 | 0.993 | 1.258 | 0.405 | 0.996 |
| F8 | 21.618 | 1.379 | 0.910 | 1.952 | 0.017 | 0.992 | 3.886 | 12.117 | 0.993 | 1.243 | 0.414 | 0.994 |
| F9 | 22.691 | 1.366 | 0.898 | 1.949 | 0.018 | 0.989 | 4.621 | 12.112 | 0.989 | 1.263 | 0.404 | 0.987 |

$F_1$ to $F_9$ are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope.

mulations $F_1$ to $F_9$ are shown in Table 5. Polynomial equation for $3^2$ full factorial designs is given in Equation

$$Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1{}^2+b_{22} X_2{}^2 \ldots$$

Where, Y is dependent variable, $b_0$ arithmetic mean response of nine batches, and $b_1$ estimated co-efficient for factor $X_1$. The main effects ($X_1$ and $X_2$) represent the average result of changing one factor at a time from its low to high value. The interaction term ($X_1X_2$) shows how the response changes when two factors are simultaneously changed. The polynomial terms ($X_1{}^2$ and $X_2{}^2$) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check Point Formulations of Intermediate concentration ($C_1$, $C_2$). The equations for Wetting time, disintegrating time, $t_{50\%}$ and $t_{90\%}$ developed as follows,

$$Y_1= 44.938-13.183X_1-5.402X_2+1.035X_1X_2+4.297X_1{}^2+1.762X_2{}^2$$
(for Wetting time)

$$Y_2= 31.176-8.772X_1-3.94X_2+0.2\ X_1X_2+1.56\ X_1{}^2+2.024\ X_2{}^2$$
(for Disintegration time)

$$Y_3= 12.575-4.094X_1-1.117X_2-1.023 X_1X_2+1.057 X_1{}^2-1.247 X_2{}^2 \text{ (for } t_{50\%})$$

$$Y_4= 41.788-13.606X_1-3.712X_2-3.399 X_1X_2+3.515 X_1{}^2-4.145 X_2{}^2 \text{ (for } t_{90\%})$$

The positive sign for co-efficient of $X_1$ in $Y_1$, $Y_2$, $Y_3$ and $Y_4$ equations indicates that, as the concentration of Crospovidone decreases, Wetting time,

**Table 5: Dissolution Parameters of Pravastatin Fast Dissolving Tablets $3^2$ Full Factorial Design Batches**

| Formulation Code | Kinetic Parameters | | | |
| --- | --- | --- | --- | --- |
| | $t_{50\%}$ or $t_{1/2}$ | $t_{90\%}$ | WT(Sec) | DT(Sec) |
| $F_1$ | 6.573 | 21.843 | 31.05 | 21.53 |
| $F_2$ | 9.546 | 31.720 | 33.94 | 23.11 |
| $F_3$ | 10.382 | 34.498 | 34.57 | 24.13 |
| $F_4$ | 9.546 | 31.720 | 34.03 | 23.72 |
| $F_5$ | 13.344 | 44.341 | 36.93 | 25.33 |
| $F_6$ | 12.722 | 42.274 | 55.26 | 41.36 |
| $F_7$ | 17.009 | 56.522 | 55.29 | 38.48 |
| $F_8$ | 17.331 | 57.592 | 60.42 | 41.04 |
| $F_9$ | 16.726 | 55.582 | 62.95 | 41.88 |
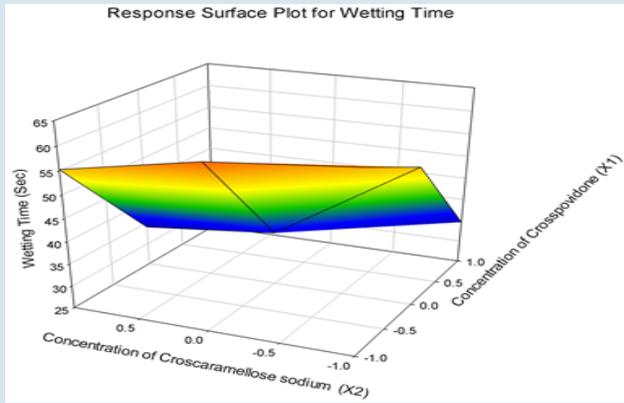
**Figure 7:** Response Surface Plot for Wetting Time.
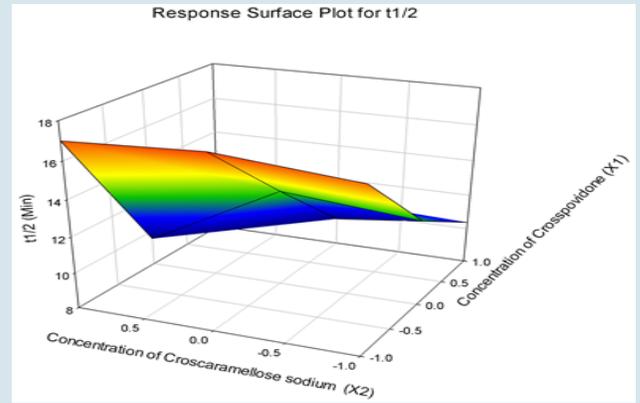


**Figure 9:** Response Surface Plot fort 50%.
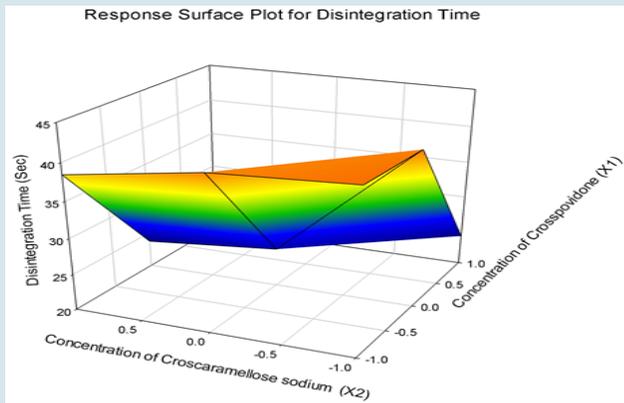


**Figure 8:** esponse Surface Plot for Disintegration Time.
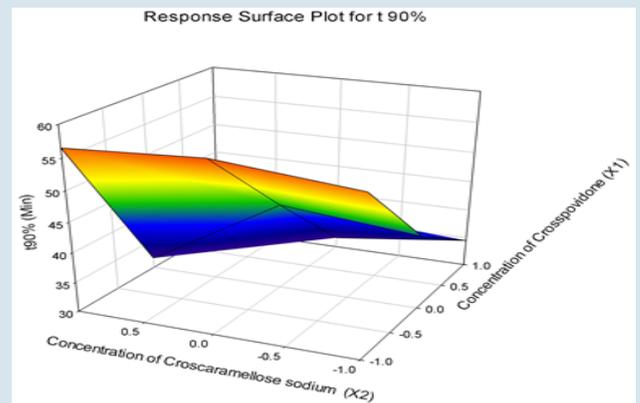


**Figure 10:** Response Surface Plot for $t_{90\%}$.

**Table 6: Dissolution Parameters for Predicted and Observed Values for Check Point Formulations**

| Formulation Code | Predicted Value | | | | Actual Observed Value | | | |
|---|---|---|---|---|---|---|---|---|
| | WT (Sec) | DT (Sec) | $t_{50\%}$ (min) | $t_{90\%}$ (min) | WT (Sec) | DT (Sec) | $t_{50\%}$ (min) | $t_{90\%}$ min |
| C1 | 56.004 | 38.478 | 14.878 | 49.440 | 56.53 | 39.12 | 14.68 | 49.57 |
| C2 | 37.419 | 25.766 | 9.667 | 32.122 | 38.52 | 26.21 | 9.59 | 32.78 |

Disintegrating time, $t_{50\%}$ and $t_{90\%}$ value increases. In other words, the data demonstrate that both $X_1$ (Quantity of Crospovidone) and $X_2$ (Quantity of Croscarmellose sodium) affect the time required for drug release (Wetting time Disintegrating time, $t_{50\%}$ and $t_{90\%}$). From the results, it can be concluded that, and increase in the Quantity of the Superdisintegrant leads to decrease in Disintegration time of the Dosage form and drug release pattern may be changed by appropriate selection of the $X_1$ and $X_2$ levels. The Dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarized in Table 6. The closeness of Predicted and Observed values for Wetting time, disintegrating time $t_{50\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. The Response Surface Plots were presented to show the effects of $X_1$ and $X_2$ on Wetting time, Disintegrating time $t_{50\%}$ and $t_{90\%}$. The final best (Optimized) formulation $(F_1)$ is compared with marketed product (**PRAVACHOL-40**) shows similarity factor $(f_2)$ 89.724, difference factor $(f_1)$ 1.307 (There is no significant difference in drug release because $t_{cal}$ is<0.05).

## CONCLUSION

The present research work envisages the applicability of Superdisintegrants such as Crospovidone and Croscarmellose sodium in the design and development of Fast Dissolving tablet formulations of Pravastatin utilizing the $3^2$ factorial design. From the results, it was clearly understand that as the concentration of Superdisintegrant increases the release rate of drug was RAPID and both of these Superdisintegrants can be used in combination since do not interact with the drug which may be more helpful in achieving the desired fast Dissolving of the dosage form for rapid action and improved Bioavailability. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, first order release type. Based on evaluation parameters, the optimized formulation $F_1$ may be used for the effective management of hypercholesterolemia and to reduce the risk of cardiovascular disease. This may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation.

## ACKNOWLEDGEMENTS

## CONFLICT OF INTEREST

None

## ABBREVIATIONS AND SYMBOLS USED

ODT: Oral Disintegrating Tablet; FDT: Fast Dissolving Tablet; CoA: Coenzyme A; Kg: Kilogram; Cm: Centimeter; %: Percentage; Mg: Milligram; ML: Millilitre; %CDR: Percentage Cumulative Drug Release; BCS: Biopharmaceutical Classification; UR: UN Released; Min: Minute; $^oC$: Degree Centigrade; Mm: millimeter; T1/2: Half Life; $t_{90\%}$: Time taken to release 90% drug from dosage form; WT: Wetting time; DT: Disintegration time.

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## PICTORIAL ABSTRACT
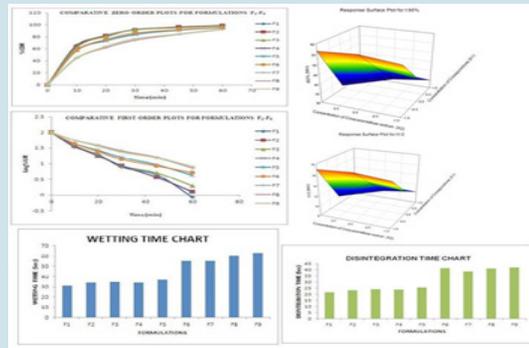


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