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Original Article

Formulation Development and Evaluation of Clopidogrel Fast Dissolving Tablets

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Abstract

The main objective of the present research work is to formulate the Clopidogrel Fast Dissolving tablets. Clopidogrel, an antiplatelet drug, belongs to BCS Class-II and used to control Heart attack, Hypertension by inhibiting Platelet activation and aggregation .The Fast Dissolving tablets of Clopidogrel were prepared employing different concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Superdisintegrant 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. Totally nine formulations were designed and evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, and *in-vitro* drug release. From the Results it was 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 into different Kinetic models, the statistical parameters like intercept (a), slope (b) and regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, $t_{50\%}$, $t_{90\%}$. Validity of developed polynomial equations was verified by designing 2 check point formulations (C_1, C_2). According to SUPAC guidelines, the formulation (F_5) containing combination of 15% Crospovidone and 15% Croscarmellose, is the most similar formulation (similarity factor f_2=91.3936, dissimilarity factor f_1= 1.203& No significant difference, t= -0.00062) to marketed product (PLAVIX-75). The selected formulation (F_1) follows First order, Higuchi's kinetics, mechanism of drug release found to be Fickian Diffusion (n= 0.226).

Keywords : Clopidogrel, 3^2Factorial Design, super disintegrants, Crospovidone , croscarmellose Sodium, Wetting Time, Disintegration Time, Fickian Diffusion.

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1. 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. It is also for active patients who are busy, travelling and may not have access to water. Fast dissolving tablets are also known as oro dispersible 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 oro dispersible tablets. They vary from analgesics to neuroleptics and anti-psychotic drugs. However, only a small percentage of them are researched on and some have been manufactured and marketed.

Fast-dissolving drug-delivery systems were initially developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experiences difficulties in swallowing traditional oral solid-dosage forms [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 oro dispersible dosage forms are progressively being recognized in both, industry, and academics [2, 3].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 [4]. The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick intake of water into the tablet matrix, which creates porous structures and result in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation. Orally disintegrating tablets 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, direct compression) [5].

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

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.

1.1. Drug Profile and Rationality for Experimental Design

Clopidogrel, a weak base known chemically as Methyl (S)- α- (2chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1)].It is practically insoluble in water at neutral pH, freely soluble in aqueous buffer at pH 1, and in methanol, sparingly soluble in methylene chloride, and practically insoluble in ethyl ether [6].Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. The blockade of inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. Platelet inhibition can be demonstrated 2 h after a single dose of oral Clopidogrel, but the onset of action is slow(so that a loading-dose of 300-mg is followed by 75 mg once daily).The active metabolite has an elimination half-life of about six hours and acts by forming a disulfide bridge with the platelet ADP receptor [7-10].

According to the biopharmaceutics classification system (BCS), Clopidogrel is categorized as a class II agent (poorly water soluble and highly permeable) its solubility is very low (i.e., 0.0099 mg/ml) and has very low bioavailability [6]. Oral bioavailability of clopidogrel is very low (less than 50%), due to poor water solubility.Hence, the drug is selected for formulating Fast Dissolving Tablets by Direct compression method.

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 [11-14].

Hence an attempt is made in this research work to formulate Fast Dissolving Tablets of Clopidogrel 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)

2. Materials and Methods

Materials used in this study were obtained from the different sources. Clopidogrel was a gift sample from Dr.Reddy's Laboratories, Hyderabad, India. Avicel pH-101, Crospovidone, Croscarmellose, were procured from Loba ChemiePvt.Ltd, Mumbai. Other excipients such as Magnesium Stearate and talc were procured from S.D. Fine Chem. Ltd., Mumbai.

2.1. Formulation Development of Clopidogrel 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 [15].

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 Clopidogrel 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 7.5%, 10.0%, 15%,three levels of factor X_2 (Croscarmellose) at a concentration of 7.5%, 10.0%, 15%. (% with respect to average weight of Tablet, i.e200 mg) were taken as the rationale for the design of the Clopidogrel Fast Dissolving tablet formulation. Totally nine Clopidogrel Fast Dissolving tablet formulations were prepared employing

selected combinations of the two factors i.e, X1, X_2 as per 3^2 Factorial and evaluated to find out the significance of combined effects of X1, 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.

2.2. Preparation of Clopidogrel Fast Dissolving Tablets

Clopidogrel Tablets were prepared by direct compression method. The composition of each tablet is shown in Table No 2. The drug, diluents, and superdisitegrants 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 a 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.

2.2.1. 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= 7.5%, 0=10.0%, +1=15%. Three levels for the Concentration of Croscarmellose sodium were selected and coded as -1= 7.5%, 0=10.0%, +1=15%. Formulae for all the experimental batches were given in Table 2 [16].

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

2.3. Evaluation of Clopidogrel Fast Dissolving Tablets

2.3.1. 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 [17].

2.3.2. Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). 20 Tablets were taken and weighed, and also initial weight was noted (W_0)

dedusted in a drum for a fixed time (100 revolutions, in a Roche Friabilator) and they were 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 % [17].

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

2.3.3. 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 115% (100±15%) of the labeled drug content can be considered as the test passed [17].

2.3.4. Assay

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The powder equivalent to 100 mg Clopidogrel was weighed and dissolved in 10 ml of Distilled water in volumetric flask, the volume was adjusted to 100 ml with Phosphate buffer pH 6.8 and the solution was filtered. An aliquot of 1.0 ml of solution was diluted to 10 ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content was determined spectrophotometrically at 324 nm [6].

2.3.5. Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers [17].

2.3.4. 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 [18-19].

2.3.5. In-vitro Dissolution Study

The *in-vitro* dissolution study for the Clopidogrel 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 the same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 324 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3) [6].

2.3.6. Disintegration Test

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva; however amount 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

screen 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.

2.3.7. Kinetic Modeling of Drug Release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release [21-24].

3. Results and Discussion

Fast Dissolving tablets of Clopidogrel 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 100 mg of Clopidogrel 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

Table 2. Formulae for the preparation of Clopidogrel 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**
Clopidogrel	75	75	75	75	75	75	75	75	75
Avicel pH-101	71	76	81	76	81	86	81	86	91
Crospovidone	25	25	25	20	20	20	15	15	15
Croscarmellose sodium	25	20	15	25	20	15	25	20	15
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight	200	200	200	200	200	200	200	200	200

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 3.175±0.13-3.375±0.15 Kg/cm^2. Weight loss in the friability test was not more than 0.67%. Drug content of prepared tablets was within

Table 3. Post-compression parameters for the formulations**.**

S.No	Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation(mg)	Drug Content (%)	Wetting Time(sec)	Disintegration Time (sec)
1	F_1	3.375±0.15	4.79±0.14	0.6±0.2	200.71±0.9	99.86±0.25	20.59±1.4	10±1.4
2	F_2	3.29±0.14	4.825±0.16	0.66±0.3	201.48±1.9	99.69±0.70	20.66±1.5	11±1.5
3	F_3	3.29±0.15	4.76±0.15	0.64±0.1	200.69±1.1	99.68±0.50	22.91±1.7	11±1.7
4	F_4	3.275±0.15	4.765±0.10	0.64±0.2	200.57±2.2	99.78±0.40	22.50±1.3	11±1.3
5	F_5	3.175±0.13	4.8±0.12	0.54±0.3	201.50±1.1	99.61±0.90	22.58±1.4	12±1.4
6	F_6	3.18±0.15	4.735±0.11	0.67±0.04	201.06±2.0	99.60±0.70	24.23±1.6	13±1.6
7	F_7	3.378±0.16	4.715±0.12	0.63±0.3	200.50±1.4	99.20±0.25	22.32±1.3	11±1.3
8	F_8	3.275±0.14	4.75±0.12	0.54±0.4	199.70±0.3	99.03±0.70	22.40±1.35	12±.1.4
9	F_9	3.28±0.16	4.685±0.11	0.64±0.4	200.47±0.9	99.03±0.5	24.65±1.6	13±1.6

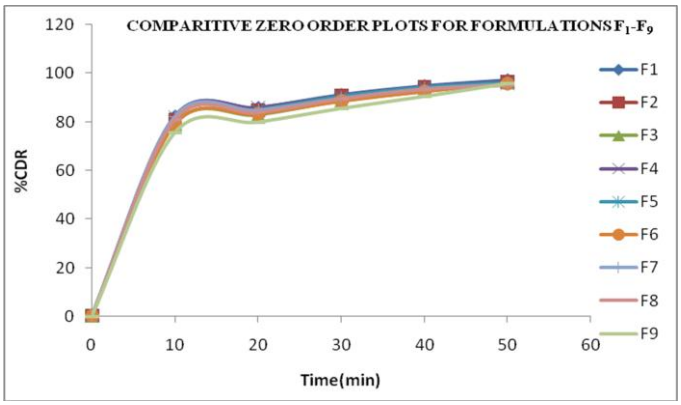

Figure1. Comparative zero order plots for formulation f_1-f_9.

acceptance range only. The wetting time of tablets was in the range of 20.59±1.4-24.65±1.6 sec. The disintegration time of tablets was in the range of 10±1.4-13±1.6 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 and wetting time chart, disintegration time charts were shown in figure 2-3 respectively.The dissolution parameters are given in Table 4. Cumulative % Drug release of factorial design formulations F_1-F_9 at 1 Hr was found to be in the range of 94.95-97.145 **%**. 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, showing various disintegration mechanism such as wicking and swelling etc more compared with lower concentration and alone, drug may release rapidly and shows improved bioavailability. Therefore, required release of drug can be obtained by

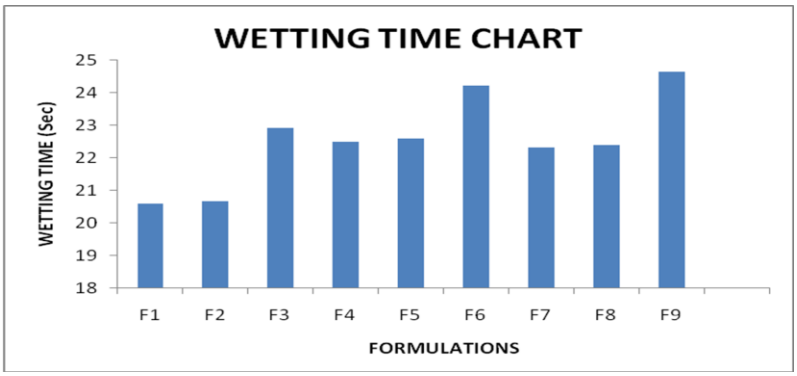

Figure 2.Wetting time chartfor formulation F_1-F_9.

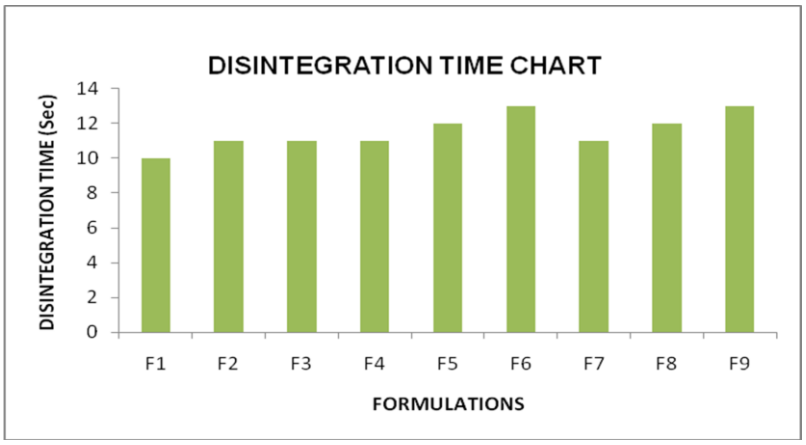

Figure 3. Disintegration time chart for formulation F_1-F_9.

Table 4. Regression analysis data of 3^2 factorial design formulations of Clopidogrel fast dissolving tablets.

S.NO	Formulation Code	KINETIC PARAMETERS											
		ZERO ORDER			FIRST ORDER			HIGUCHI			KORSMEYER-PEPPAS		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	37.423	1.510	0.759	1.767	0.027	0.955	16.579	13.263	0.914	0.226	1.405	0.866
2	F_2	36.744	1.511	0.765	1.771	0.026	0.955	16.094	13.227	0.917	0.230	1.406	0.867
3	F_3	35.625	1.509	0.774	1.794	0.025	0.956	15.386	13.118	0.923	0.239	1.408	0.870
4	F_4	37.516	1.500	0.756	1.753	0.026	0.948	16.691	13.202	0.912	0.219	1.401	0.865
5	F_5	36.838	1.501	0.762	1.759	0.025	0.947	16.205	13.166	0.916	0.224	1.402	0.866
6	F_6	35.718	1.499	0.771	1.782	0.024	0.950	15.498	13.057	0.921	0.232	1.403	0.869
7	F_7	37.441	1.478	0.752	1.739	0.024	0.932	16.795	13.038	0.909	0.210	1.392	0.865
8	F_8	36.762	1.479	0.758	1.748	0.023	0.933	16.310	13.001	0.913	0.215	1.393	0.867
9	F_9	33.450	1.514	0.794	1.832	0.024	0.959	13.919	12.989	0.934	0.260	1.415	0.875
10	MP	37.363	1.513	0.759	1.744	0.026	0.946	16.399	13.307	0.915	0.223	1.404	0.861

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.

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 25 mg of Crospovidone, 25 mg of Croscarmellose sodium showed promising dissolution parameter (wetting time= 20.59±1.4sec, disintegrating time = 10±1.4sec, $t_{50\%}$ = 11.070min, $t90_{\%}$ = 36.785 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 Clopidogrel 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 (R^2) values in the range of 0.932-0.956. The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.909-0.934, 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 0.210-0.260 that shows Fickian diffusion mechanism. Polynomial equations were derived for wetting time, disintegrating time,

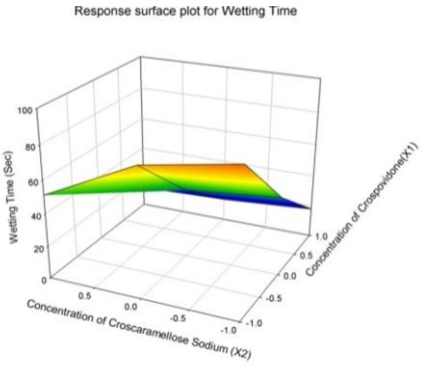

Figure 4. Response Surface plot for Wetting Time.

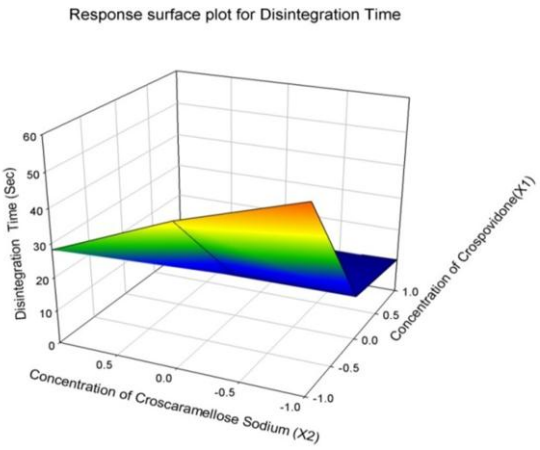

Figure 5. Response surface plot for disintegration time.

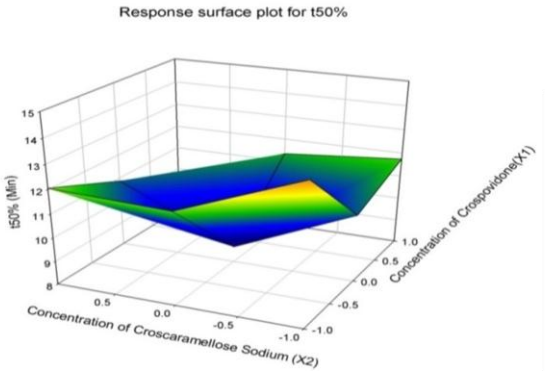

Figure 6. Response Surface plot for $t_{50\%}$.

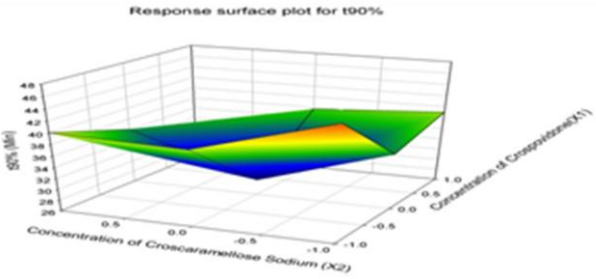

Figure 7. Response Surface plot for $t_{90\%}$.

$t_{50\%}$, 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 figure 4-7 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 formulations 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.

$$Y_1= 22.538-0.808X_1-1.063X_2+0.0025X_1X_2-0.808\ X_1^2+0.986X_2^2 \text{(for Wetting time)}$$

Y_2= 11.556-0.667X_1-0.833X_2+0.25 X_1X_2-0.667 X_1^2-0.167 X_2^2(for Disintegration time)

Y_3= 12.16-0.617X_1-0.328X_2-0.256 X_1X_2+0.104 X_1^2-0.125 X_2^2(for $t_{50\%}$)

Y_4 = 40.393-2.050X_1-1.09X_2-0.851 X_1X_2+0.345 X_1^2-0.418 X_2^2(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, disintegrating time, $t_{50\%}$, and $t_{90\%}$ value increases. In other words, the data demonstrate that both X_1 (amount of Crospovidone) and X_2 (amount 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 an increase in the amount 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

Table 5. Dissolution parameters of Clopidogrel fast dissolving tablets 3^2 full factorial design batches.

S.NO	FORMULATION CODE	KINETIC PARAMETERS			
		t1/2 (Min)	t90% (Min)	WT(Sec)	DT(Sec)
1	F_1	11.070	36.785	20.59	10
2	F_2	11.570	38.446	20.66	11
3	F_3	12.081	40.144	22.91	11
4	F_4	11.610	38.579	22.50	11
5	F_5	12.068	40.103	22.58	12
6	F_6	12.581	41.807	24.23	13
7	F_7	12.677	42.126	22.32	11
8	F_8	13.081	43.467	22.40	12
9	F_9	12.664	42.083	24.65	13
10	MP	11.573	38.457	18.98	10

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)
C_1	23.509	12.16	12.560	41.732	23.619	12.28	12.652	41.898
C_2	21.638	10.66	11.614	38.592	21.690	10.93	11.721	39.012

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_5) is compared with marketed product (PLAVIX-75) shows similarity factor (f_2) and 91.3936, difference factor (f_1) 1.203 (There is no significant difference in drug release (becauset$_{cal}$ <0.05).

4. 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 Clopidogrel utilizing the 3^2 factorial design. From the results it was clearly understood that as the concentration of Superdisintegrant increases the release rate of drug was RAPID (Improved Solubility) 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 Fickian diffusion, first order release type. On the basis of evaluation parameters, the optimized formulation F_1 may be used for the effective management of Acute Coronary Syndrome (ACS), Hypertension, Heart Attack, and Stroke. This may improve the patient compliance by showing rapid action via disintegration without difficulty 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.

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