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RESEARCH ARTICLE

Formulation Development and Evaluation of Amisulpride Fast Dissolving Tablets

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SUMMARY

The main objective of current research work was to formulate Amisulpride fast dissolving tablets. Amisulpride, a second generation antipsychotic agent, belongs to BCS class-II drug and used to treat psychoses, paranoid, productive schizophrenias, dysthymia. Fast dissolving tablets of amisulpride were prepared employing different concentrations of crospovidone and croscarmellose sodium in different combinations as a superdisintegrants by direct compression technique using 32 factorial design. The concentration of crospovidone and croscarmellose sodium was selected as independent variables, X1 and X2 respectively whereas, wetting time, Disintegration time, t50% ,t90%were selected as dependent variables. 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, t50%, t90%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C1, C2). According to to SUPAC guidelines the formulation (F1) containing combination of 9% crospovidone and 9% croscarmellose, is the most similar formulation (similarity factor f2=85.384, dissimilarity factor f1= 2.098& No significant difference, t= 0.0585) to marketed product (SOLIAN-100). The selected formulation (F1) follows First order, Higuchi's kinetics, mechanism of drug release was found to be Non-Fickian Diffusion Super Case-II Transport (n= 1.445).

Key Words: *Amisulpride, 32 factorial design, super disintegrants, Wetting time, Disintegration time, Non-Fickian diffusion.*

Hızlı Çözünen Amisülpirid Tabletlerin Değerlendirilmesi ve Formülasyon Geliştirilmesi

ÖZET

Mevcut araştırma çalışmalarının temel amacı, Amisulpride hızlı çözünen tabletleri formüle etmektir. Amisulpride ikinci nesil antipsikotik bir ajandır, BCS sınıf II uyuşturucuya aittir ve psikozları, paranoyak, üretken şizofreni, distimiyi tedavi etmek için kullanılır. Amisülpirid'in hızlı çözünen tabletleri, 32 faktöriyel tasarım kullanılarak doğrudan sıkıştırma tekniği ile farklı derişimlerde süper dağıtıcı olarak farklı konsantrasyonlarda krospovidon ve kroskarmeloz sodyum kullanılarak hazırlandı. Bağımlı değişken olarak krospovidon ve kroskarmeloz sodyum konsantrasyonu sırasıyla bağımsız değişken X1 ve X2 olarak seçilirken ıslanma süresi, parçalanma zamanı, t5o%, t90% seçildi. Dokuz formülasyon tasarlanmış ve sertlik, ufalanabilirlik, kalınlık, ıslatma süresi, parçalanma süresi, in-vitro ilaç salınımı için değerlendirilmiştir. Sonuçlardan, tüm formülasyonun farmakope sınırları içinde olduğu ve tüm formülasyonların in-vitro çözünme profillerinin farklı kinetik modellere uyduğu, kesişim noktası (a), eğim (b) ve regresyon katsayısı (r) hesaplandı. Islatma süresi, parçalanma süresi, t50%, t90% için polinomiyal denklemler geliştirildi. Geliştirilmiş polinom denklemlerinin geçerliliği, 2 kontrol noktası formülasyonu (C1, C2) tasarlayarak doğrulanmıştır. SUPAC kılavuzlarına göre, % 9 krospovidon ve % 9 kroskarmellozun kombinasyonunu içeren formülasyon (F1), pazarlanmış ürüne en benzer formülasyondur (benzerlik faktörü f2 = 85.384, farksızlık faktörü f1 = 2.098 ve önemli fark yok, t = 0.0585)(Amisülpirid-100). Seçilen formülasyon (F1) takip edildi. Birinci mertebeden, Higuchi'nin kinetiği, ilaç salınım mekanizması Non-Fickian Difüzyon Süper Durum II Nakil (n = 1.445) olarak bulundu.

Anahtar Kelimeler: *Amisülpirid, 32 faktöryel tasarım, süper dağıtıcılar, Islanma zamanı, Dağılma zamanı, Non Fickian difüzyon.*

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INTRODUCTION

Fast dissolving tablets are suitable for numerous kind of people , including for people who have swallowing difficulties, pediatric, geriatric, and bedridden patients. They are also useful for active patients who are busy, travelling and may not have access to water. Fast dissolving tablets are also popular as orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc (Kavitha et al., 2013).

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, 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 (Thanda venkataramudu et al., 2012).

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.

Amisulpride is a benzamide analogue. The chemical name of Amisulpride is 4-Amino-N-[[(2RS)-1-thylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide (Nirvesh Chaudari et al., 2015; Hitesh P. Dalvadi et al., 2016). It blocks cerebral dopamine D_2 and D_3 receptors. When administered at an oral daily dose of 50 mg, it improves the dopaminergic neurotransmission with a D_2 dopaminergic receptors pre-synaptic inhibition and it is used in the treatment of schizophrenia. Amisulpride ODT which when placed in the tongue disintegrates or dissolves rapidly in the saliva without the need of drinking water. As tablet disintegrates in the mouth, this could enhance the clinical effect of the drug through pregastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism (M.A.Shende et al., 2014).

It is an important task to design an optimized formulation with an appropriate dissolution rate in a short time period with a minimum number of trials or runs. 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 rapid release dosage forms (Schwartz BJ et al., 1996; Raghavendra Kumar Gunda ., 2015).

Hence an attempt is made in this research work to formulate Fast Dissolving Tablets of Amisulpride using crospovidone and croscarmellose sodium. Instead of normal heuristic 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 dosage form. The fast dissolving tablets formulation by direct compression method is most acceptable in industrial 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. Amisulpride was a gift sample from Dr.Reddy's Laboratories, Hyderabad, India. Avicel pH-101, crospovidone, croscarmellose, were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as magnesium stearate, talc, vanillin and sucralose were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation development of amisulpride fast dissolving tablets:

The factorial design is a technique that allows identification of factors involved in a methodology and assesses their relative priority. 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 (Ramji Anil Kumar Arza et al., 2016; NG RaghavendraRao et

al., 2010).

A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables Crospovidone and Croscarmellose sodium are used in formulation of Amisulpride 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 9%, 7%, 5%.Three levels of factor X_2 (croscarmellose) at a concentration of 9%, 7%, 5%. (% with respect to average weight of tablet, i.e 200 mg) was taken as the rationale for the design of the Amisulpride fast dissolving tablet formulation. Amisulpride fast dissolving tablet formulations were prepared employing selected combinations of the two factors i.e, X_1, X_2 as per 3^2 factorial design 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 Amisulpride Fast Dissolving Tablets:

Amisulpride tablets were prepared by direct compression method. The composition of each tablet is shown in Table No 2. The drug, diluents, superdisitegrants were passed through sieve #60 separately. 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.

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= 5%, 0=7%, +1=9%. Three levels for the concentration of croscarmellose sodium were selected and coded as -1= 5%, 0=7%, +1=9%. Formulae for all the experimental batches were given in Table 2 (Schwartz BJ et al., 1996; Shiv Shankar Hardenia et al., 2014).

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 Amisulpride 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
Amisulpride	100	100	100	100	100	100	100	100	100
Avicel pH-101	50	54	58	54	58	62	58	62	66
Crospovidone	18	18	18	14	14	14	10	10	10
Croscarmellose sodium	18	14	10	18	14	10	18	14	10
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Sucralose	3	3	3	3	3	3	3	3	3
Vanillin	1	1	1	1	1	1	1	1	1
Total Weight	200	200	200	200	200	200	200	200	200

Evaluation of amisulpride 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.

Friability

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

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 92.5% or not more than 107.5% (100±7.5%) of the labeled drug content can be considered as the test was passed.

Assay

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The powder equivalent to 100 mg Amisulpride 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 were diluted to 10 ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content was determined spectrophotometrically at 226 nm.

Thickness

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

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.

In vitro dissolution study

The *In vitro* dissolution study for the Amisulpride 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 226 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

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 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. 6 tablets were chosen randomly from the composite samples and the average value was determined.

Kinetic modelling 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 (Notari RE., 1987;Higuchi., 1963; Peppas., 1985).

RESULTS AND DISCUSSION

Fast dissolving tablets of Amisulpride were prepared and optimized by 3^2 factorial design in order to select the best composition of 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. 9 formulations were prepared using 3 levels of 2 factors and all the formulations containing 100 mg of Amisulpride 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 as per official methods and results are given in Table 3. The hardness of tablets was in the range of 3.31±0.57-3.81±0.28 Kg/cm^2. Weight loss in the friability test was not more than 0.63%. Drug content of prepared tablets was within acceptance range only. The wetting time of tablets was in the range of 25.5±1.3-90.0±1.6 sec. The disintegration time of tablets was in the range of 35.5±1.5-106.0±1.7 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 Fig.1-4 (kinetic plots), wetting time chart, disintegration time charts were shown in Fig.5-6.

The dissolution parameters are given in Table 4. Cumulative % drug release of factorial design formulations F_1-F_9 at 25 mins were found to be in the range of 89.06-99.33 %. 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 18 mg of crospovidone, 18 mg of croscarmellose sodium showed promising dissolution parameter (Wetting time$_=$ 25.5±1.3sec, Disintegrating time $_=$ 35.5±1.5 sec , $t_{50\%}$ $_=$ 2.679 min , $t_{90\%}$ $_=$ 8.902 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 Amisulpride 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 0.974-0.999. The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.958-0.994, 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 0.871-1.479 that shows Non-Fickian diffusion mechanism with super case-II transport system.

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 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,

$Y_1= 49.00-13.25X_1-19X_2+8.75 X_1^2+17.5 X_2^2$ (for Wetting time)

$Y_2= 62.33-16.25X_1-19X_2+11.75 X_1^2+13.5 X_2^2$ (for Disintegration time)

$Y_3= 3.441-0.605X_1-0.331X_2+0.017 X_1X_2+0.407 X_1^2+0.07 X_2^2$ (for $t_{50\%}$)

$Y_4 = 11.435-2.01X_1-1.099X_2+0.057 X_1X_2+1.35 X_1^2+0.233 X_2^2$ (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 Disintegrat-

ing 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 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 (SOLIAN-100) shows similarity factor (f_2) 85.384, difference factor (f_1) 2.098 (There is no significant difference in drug release because $p<0.05$). Comparative dissolution plots for best formulation (F_1) and marketed product shown in fig 11.

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 Amisulpride 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 (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 Non-Fickian diffusion with super case-II transport, first order release type. On the basis of evaluation parameters, the optimized formulation F_1 may be used for the effective management of psychoses, paranoid, productive schizophrenias, dysthymia. 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.

Table 3: Post-compression parameters for the formulations (± indicates standard deviation)

S.No	Formulation Code	Hardness (kg/cm^2) n=3	Thickness (mm) n=3	Friability (%) n=3	Drug Content (%) n=3	Wetting Time(sec) n=3	Disintegration Time (sec) n=3
1	F_1	3.49±0.38	3.11±0.16	0.575±0.12	99.24±0.25	25.5±1.3	35.5±1.5
2	F_2	3.41±0.57	3.08±0.76	0.585±0.13	98.68±0.30	27±1.4	41.0±1.6
3	F_3	3.65±0.42	3.06±0.44	0.465±0.1	97.85±0.50	63.5±1.6	73.5±1.8
4	F_4	3.60±0.24	3.08±0.67	0.585±0.12	99.04±.40	30±1.4	40.0±1.4
5	F_5	3.55±0.43	3.05±1.27	0.595±0.13	98.48±0.90	31.5±1.5	45.5±1.5
6	F_6	3.81±0.28	3.03±0.95	0.475±0.05	97.65±0.70	68±1.7	78.01±1.7
7	F_7	3.35±0.38	3.07±0.54	0.375±0.13	98.72±0.25	52±1.3	68.0±1.4
8	F_8	3.31±0.57	3.04±1.14	0.385±0.13	98.16±0.30	53.5±1.5	73.5±1.5
9	F_9	3.55±0.43	3.02±0.82	0.265±0.14	97.33±0.50	90±1.6	106.0±1.7

Table 4: Regression analysis data of 3^2 factorial design formulations of Amisulpride 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	18.395	7.750	0.941	2.016	0.112	0.988	0.137	29.718	0.992	1.445	0.532	0.984
2	F_2	19.434	7.340	0.932	2.000	0.103	0.999	1.209	28.452	0.994	1.459	0.504	0.986
3	F_3	10.734	7.846	0.968	2.035	0.091	0.987	5.690	29.019	0.985	1.233	0.719	0.985
4	F_4	20.315	7.295	0.922	1.993	0.105	0.994	1.788	28.469	0.990	1.466	0.500	0.977
5	F_5	21.355	6.885	0.906	1.977	0.096	0.993	3.134	27.202	0.985	1.479	0.474	0.961
6	F_6	12.656	7.391	0.956	2.018	0.086	0.996	3.765	27.769	0.988	1.255	0.688	0.979
7	F_7	9.462	7.695	0.974	2.020	0.078	0.983	6.166	28.241	0.984	1.212	0.724	0.986
8	F_8	10.504	7.284	0.973	2.010	0.073	0.998	4.818	26.973	0.991	1.228	0.694	0.993
9	F_9	1.799	7.792	0.986	2.043	0.066	0.974	11.722	27.542	0.958	0.871	1.043	0.986

Table 5: Dissolution parameters of Amisulpride fast dissolving tablets 3^2 full factorial design batches

S.NO	FORMULATION CODE	KINETIC PARAMETERS			
		$t_{1/2}$ (Min)	$t_{90\%}$ (Min)	WT(Sec)	DT(Sec)
1	F_1	2.679	8.902	25.5	35.5
2	F_2	2.922	9.711	27	41
3	F_3	3.315	11.015	63.5	73.5
4	F_4	2.872	9.545	30	40
5	F_5	3.123	10.377	31.5	45.5
6	F_6	3.515	11.681	68	78
7	F_7	3.850	12.794	52	68
8	F_8	4.138	13.750	53.5	73.5
9	F_9	4.555	15.136	90	106

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	71.688	86.268	4.033	13.395	72.03	85.75	4.128	13.524
C_2	39.438	51.018	3.097	10.295	40.02	52.34	3.121	10.351

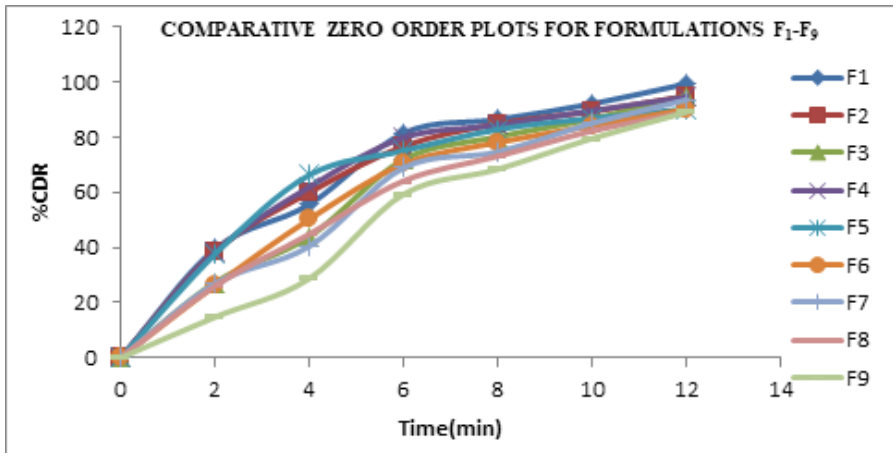

Figure 1. Comparative Zero order plots for Formulation F_1-F_9

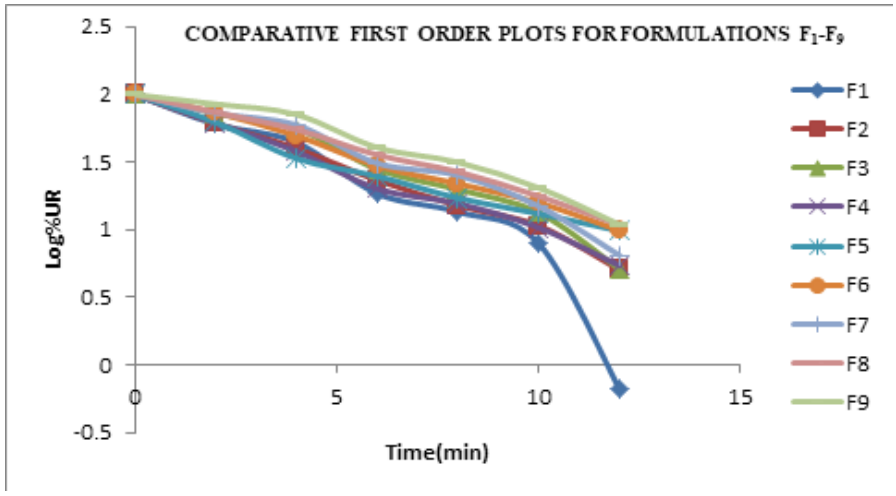

Figure 2. Comparative First order plots for Formulation F_1-F_9

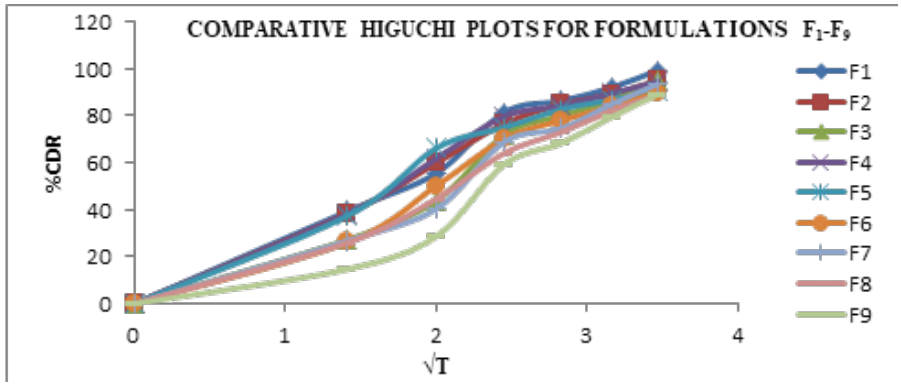

Figure 3. Comparative Higuchi plots for Formulation F_1-F_9

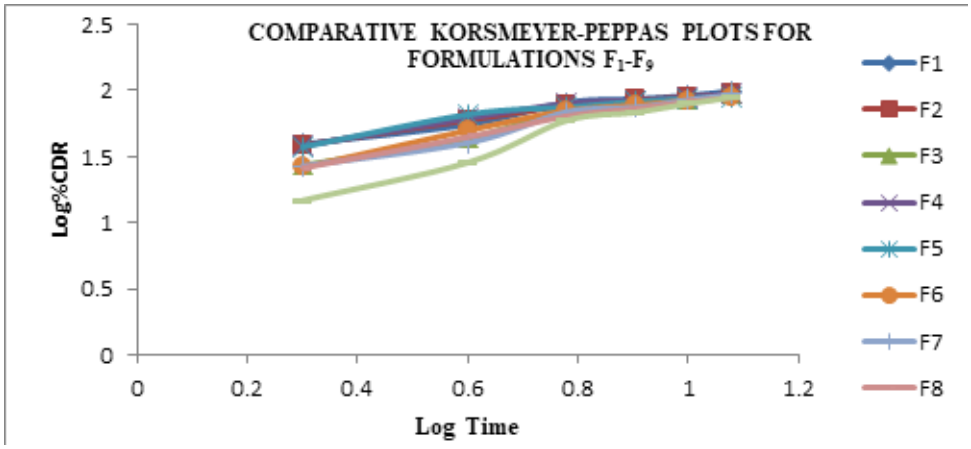

Figure 4. Comparative Korsemeyer-Peppas plots for Formulation F_1-F_9

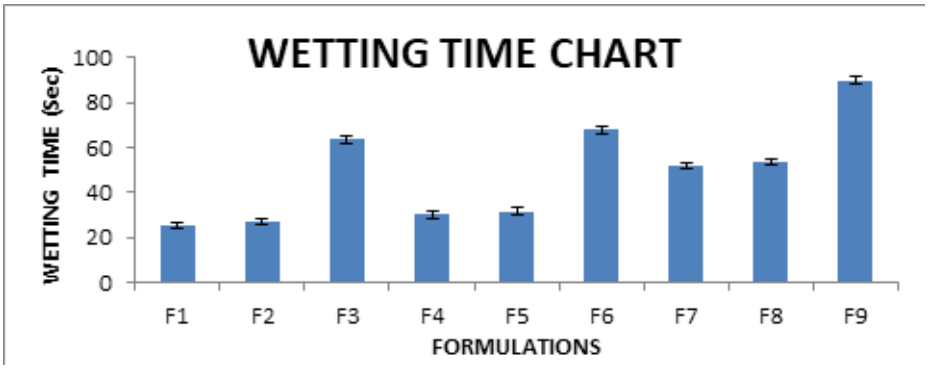

Figure 5. Wetting Time Chart for Formulation F_1-F_9

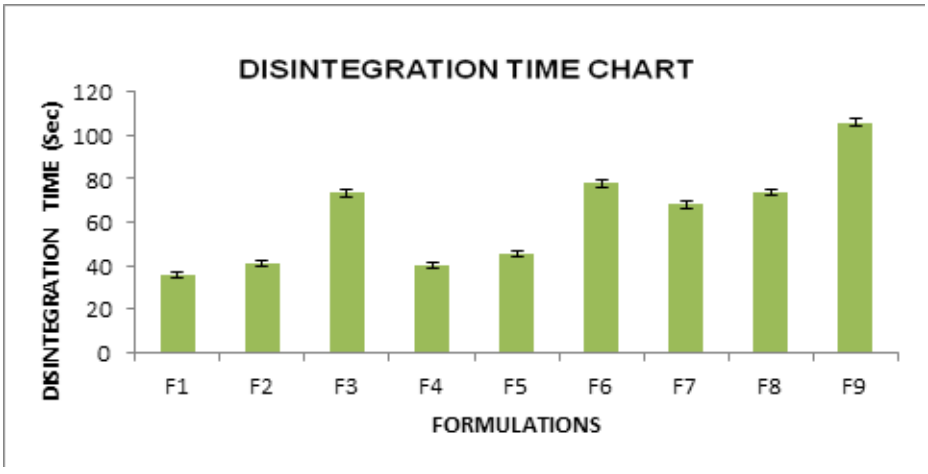

Figure 6. Disintegration Time Chart for Formulation F_1-F_9

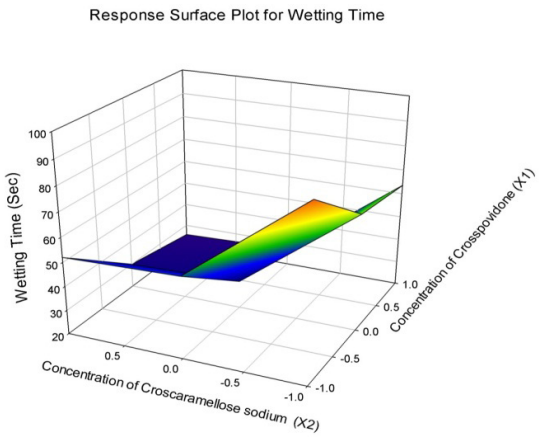

Figure 7. Response Surface plot for Wetting Time

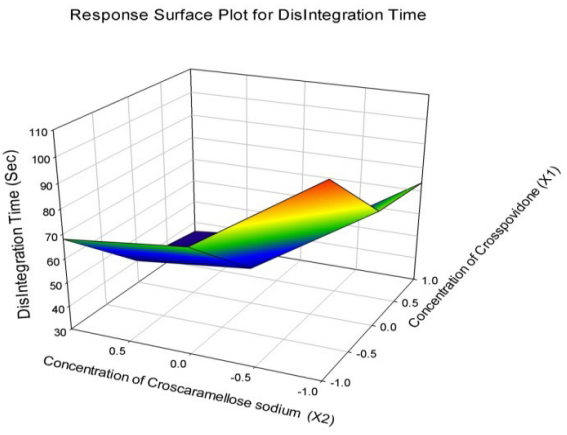

Figure 8. Response Surface plot for Disintegration Time

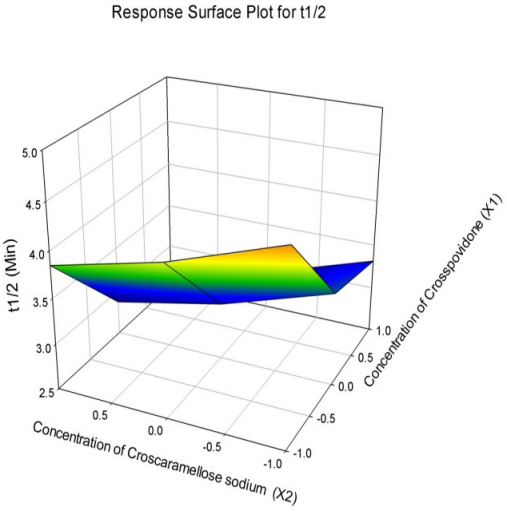

Figure 9. Response Surface plot for $t_{50\%}$

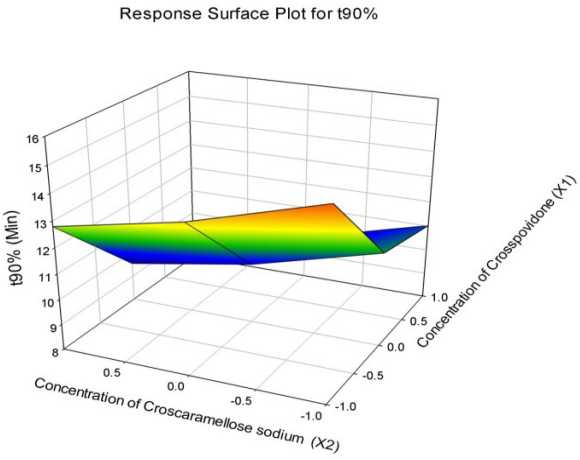

Figure 10. Response Surface plot for $t_{90\%}$

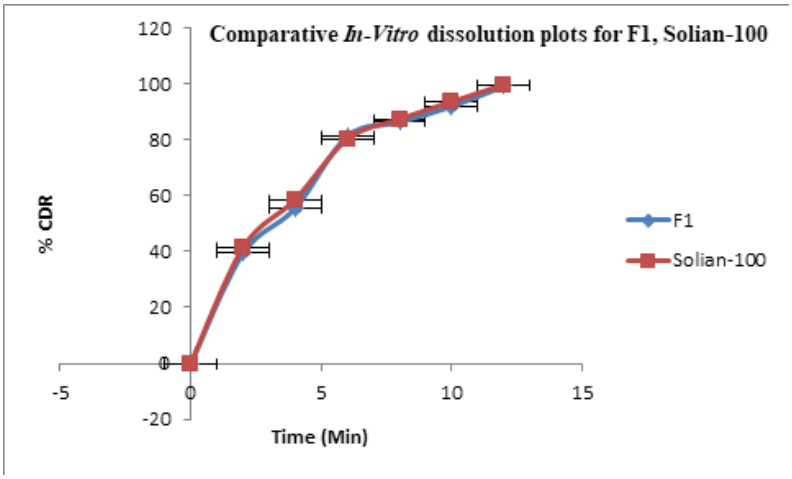

Figure 11. Comparative Dissolution plots for F_1, Solian-100

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ABBREVATIONS AND SYMBOLS USED

ODT	- Oral Disintegrating Tablet
CCS	- CrosCarmellose Sodium
CP	- Crospovidone
Kg	- Kilo Gram
Cm	- Centi Meter
%	- Percentage
mg	- milli gram
ml	- milli litre
%CDR	- Percentage Cumulative Drug Release
BCS	- Biopharmaceutical Classification
UR	- Un Released
Min	- Minute
^oC	- Degree Centigrade
mm	- milli meter
$t_{1/2}$	- Half Life
DT	- Disintegration Time
WT	- Wetting Time
$t_{50\%}$	- Time taken to release 50% drug from dosage form
$t_{90\%}$	- Time taken to release 90% drug from dosage form

Running title: Formulation and Evaluation of Fast Dissolving Tablets of Amisulpride.