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DEVELOPMENT AND CHARACTERIZATION ORAL DISINTEGRATING TABLETS OF ANTI-PSYCHOTIC DRUG USING SPRAY DRYING TECHNOLOGY

Sunil Kumar Shah*, Gaurav K. Chaurasiya, Harish Pandey, C. K. Tyagi and Neelesh Chaubey

College of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India.

***Corresponding Author: Dr. Sunil Kumar Shah**
College of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India.

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ABSTRACT
In this study, an attempt has been made to formulate oral disintegrating tablets, which are usefull for the patients suffering from panic disorder and cannot swallow solid oral dosage forms. The study included average weight, thickness, hardness, disintegration time, Wetting time, friability, In vitro drug release studies as post compression parameters and Stability study. All the formulation F1, F2, F3, F4, F5, F6 showed acceptable physicochemical properties like thickness, weight variation, hardness, drug content uniformity and *In vitro* drug release but F4 formulation showed best result in terms of disintegration time, friability, mouth feel property and wetting time due to better coating or encapsulation of superdisintegrant particle by mannitol solution in water and disintegration of tablet in particle level. So the F4 formulation was chosen as final optimized formulation. A physicochemically stable oral disintegrating formulation of drug X was successfully designed. Amongst all trials, F4 (containing 80% co-processed excipient with an ratio of polyplasdone XL10 & mannitol 25C is 1:3; inlet temperature 190-195˚C) was found to be the most suitable oral disintegrating tablet formulation. The results indicated that formulation were stable including as supported data on content uniformity and dissolution profile so it indicated that the optimized formulation was stable.

KEWWORDS: Orodispersible tablets, bioavailability, fast dissolving tablets, Terbutaline sulphate.

1. INTRODUCTION
A drug can be administered via many different routes to produce systemic pharmacological effect. The most common method of drug administration is via the oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine.[1] Oral drug delivery is the most preferred method of administrating therapeutic agents for their systemic effects.[2] Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route. When a new drug is discovered[3], one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route.[4] If patient self administration cannot be achieved, the sale of drugs constitute only small fraction of what the market would be otherwise.[1,2] Recent developments in technology have presented viable dosage alternatives for pediatric, geriatric, bedridden, nauseous or non-compliant patients who face difficulty in swallowing or chewing solid dosage forms and are unwilling to take solid preparations due to a fear of choking. Hence, orodispersible tablets are a perfect fit for them.[5] Oral disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts.[6-8] The performance of orally disintegrating tablets depends on the technology used in their manufacture. In present study we were used spray drying technology for coprocessed excipient i.e. superdisintegrant coated with mannitol with the objective to improve disintegration of oral disintegrating tablet at particle level.[8-10]

Psychosis refers to a psychiatric disorder impairing the whole personality and functioning of the individual (insight, sense of reality, delusions, and hallucinations). The main psychiatric disorders are psychoses and neuroses. There are two main types of psychoses, schizophrenia and affective psychosis/ manic-depressive psychosis.[11] Whereas the neuroses includes phobic anxiety neurosis, obsessive-compulsive disorders, dissociative-conversion disorders (hysteria) and eating disorders. It is characterized by profound disruption in cognition and emotion, affecting the most fundamental human attributes: language, thought, perception, affect and sense of self. The present study is aimed at to develop a orally disintegrating tablets of anti-psychotic drug X by spray drying technology.[12-14] This novel dosages form will disintegrate at particle level, give smooth mouth feel, quicken onset action, reduce side

/adverse effects due to its administration limited to the oral cavity, thereby by passing the liver and avoiding hepatic metabolism. Hence an increase in the therapeutic efficacy and safety of drug. The proposed work shall help to enhance bioavailability of the drug and patient compliance.[15]

2. MATERIAL AND METHOD

Terbutaline sulphate was procured as gift sample from Neuland Laboratories Limited Hyderabad and All other solvents and reagents were of analytical grade.

2.1 Evaluation of Drug powder

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends.[16] There are many formulation and process variables involved in mixing step and all these can affect the characteristics of blends produced.

2.2 Angle of Repose

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.[18] The angle of repose was determined by the funnel method suggested by Newman.

$$\theta = \tan^{-1} h/r$$

Where, θ = Angle of repose, h = height of the cone, r = Radius of the cone base

2.3 Bulk Density

Density is defined as weight per unit volume.[19] Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3. The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm^3.

$$\rho_b = M/V_p$$

Where, ρ_b = Bulk Density, M = Weight of sample in gm, V_p = Final volume of blend in cm^3

2.4 Tapped density

Tapped Density was achieved by mechanically taping the measuring cylinder containing a powder sample, after observing the initial volume[20], the tapped density may be computed and allows it to drop under its own weight a specified distance that rotate the cylinder during tapping down.

Tapped density = Mass of powder \ Volume of powder after tapping

2.5 Particle Size and Size Distribution

Particle size and size distribution of Terbutaline sulphate was determined using photomicroscope (R×LR – T) Radical India.[21] The drug particles were suspended in liquid paraffin. A drop of this suspension was spread on a glass slide and the particle size and size distribution was determined using photomicroscope.[22]

2.6 Formulation design

Design Summary

Study Type: Factorial **Runs:** 8 **Design Type:** 2 Level Factorial **Blocks:** No Blocks

Table 1: design of formulation by 2-level factorial design.

S.No.	Factor 1	Factor 2	Factor 3
1	-1.00	1.00	1.00
2	1.00	1.00	1.00
3	1.00	-1.00	-1.00
4	-1.00	1.00	-1.00
5	-1.00	-1.00	1.00
6	-1.00	-1.00	-1.00
7	1.00	1.00	-1.00
8	1.00	-1.00	1.00

Table 2: levels of independent variables

List of Super disintegrants	Higher level (+1) (in mg)	Lower level (-1) (in mg)
Crosscarmellose	6	2
Crospovidone	8	4
Sodiumstarchglycolate	10	4

2.7 Formulation design of mouth dissolving tablets by super disintegrants

Mouth dissolving tablets of Terbutaline sulphate were prepared by direct compression method using drug, sodium saccharin, flavour, talc, magnesium stearate, mannitol and microcrystalline cellulose.[23-25] Three different super disintegrants SSG (sodium starch glycollate), Croscarmellose (Ac-Di-Sol/CCS), and Crospovidone(CCP), were used in different proportions. The drug and excipients were passed through sieve (#80)

to ensure better mixing. The powders were compressed using 8 station tablet punching machine (Model KMP-8, Kambert machinery company pvt. Ltd. Ahmedabad, India) equipped with 8mm concave punches.

Ingredients used in Mouth Dissolving Tablet Preparations

Variable Ingredients: -Sodium Starch Glycolate, Crosscarmellose, Crospovidone.

Table 3: Constant ingredients for the preparation of MDTs are listed below

Name of ingredients	Quantity (in mg)
Terbutaline sulphate	5
Mannitol	10.0
Sodium Saccharin	0.2
Flavours	2.0
Magnesium stearate	1.0
Talc	2.0
MCC	q.s. to 100mg
Total	100

The batches of mouth dissolving tablet of Terbutaline Sulphate were formulated as same as control batch by using the different proportion of super disintegrants according to the factorial design.

2.9 Evaluation of Fast dissolving Tablet

Table 4: Evaluations of fast dissolving tablets

S.No	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Water absorption (%)	Wetting time (sec)	Disintegration time (sec.)	Percentage Drug release in 10 min.
1	2.8	0.63	98.63	75.6	20	150	99.26
2	3.5	0.66	99.31	72.3	22	180	102.26
3	2.9	0.61	97.13	73.5	16	80	97.76
4	2.5	0.62	97.97	72.6	11	120	98
5	3.2	0.62	97.51	74.8	17	124	98.5
6	2.1	0.61	97.32	70.8	10	60	95.55
7	2.4	0.65	98.5	75.4	16	130	98.88
8	3.4	0.64	98.05	80.5	18	150	99.5

ANOVA for selected factorial model Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F
Model significant	12.58	2.58	3	0.86	13.34
A-super disintegrant 1st	0.82	1	0.82	12.73	0.0234
B-super disintegrant 2nd	1.44	1	1.44	22.45	0.0091
C-super disintegrant 3rd	0.31	1	0.31	4.85	0.0925

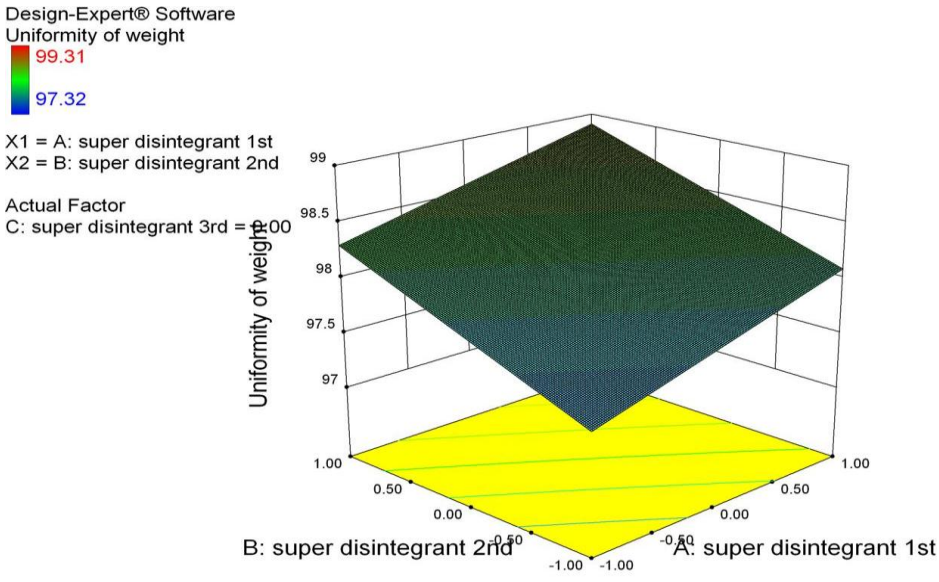

Figure 1: Uniformity of weight as a product of superdisintegrant 1st and 2nd

2.10 Disintegration Time

The test is carried out on the 6 tablets using the apparatus specified in IP distilled water at $37^0C \pm 2^0C$ was used as a disintegration media and the time in second taken for complete disinigration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.[27-28]

ANOVA for selected factorial model Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F
Model significant	10093.50	3	3364.50	28.15	0.0038
A-super disintegrant 1st	*924.50*	*1*	*924.50*	*7.74*	*0.0497*
B-super disintegrant 2nd	*3444.50*	*1*	*3444.50*	*28.82*	*0.0058*
C-super disintegrant 3rd	*5724.50*	*1*	*5724.50*	*47.90*	*0.0023*

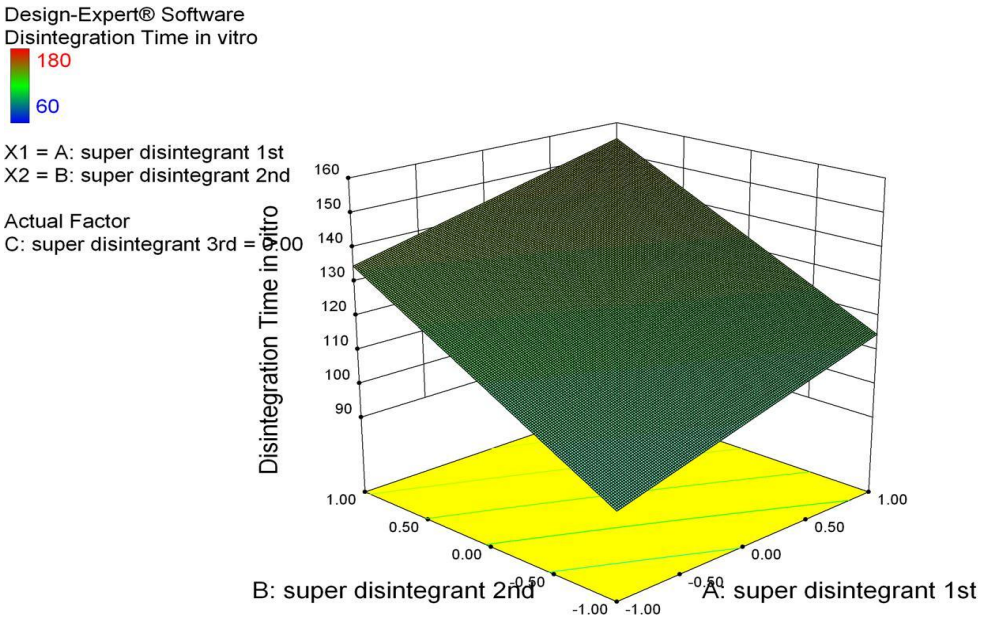

Figure 2: Disintegration time as a product of superdisintegrant 1st and 2nd

2.11 Wetting time

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined. Water absorption ratio, R was determined using following equation.[29]

R = (Wa –Wb/Wa) ×100

Where, Wa= Weight of tablet after water absorption**,** Wb=Weight of tablet before water absorption.

ANOVA for selected factorial model Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F
Model significant	104.50	3	34.83	10.72	0.0221
A-super disintegrant 1st	*24.50*	*1*	*24.50*	*7.54*	*0.0516*
B-super disintegrant 2nd	*8.00*	*1*	*8.00*	*2.46*	*0.1917*
C-super disintegrant 3rd	*72.00*	*1*	*72.00*	*22.15*	*0.0093*

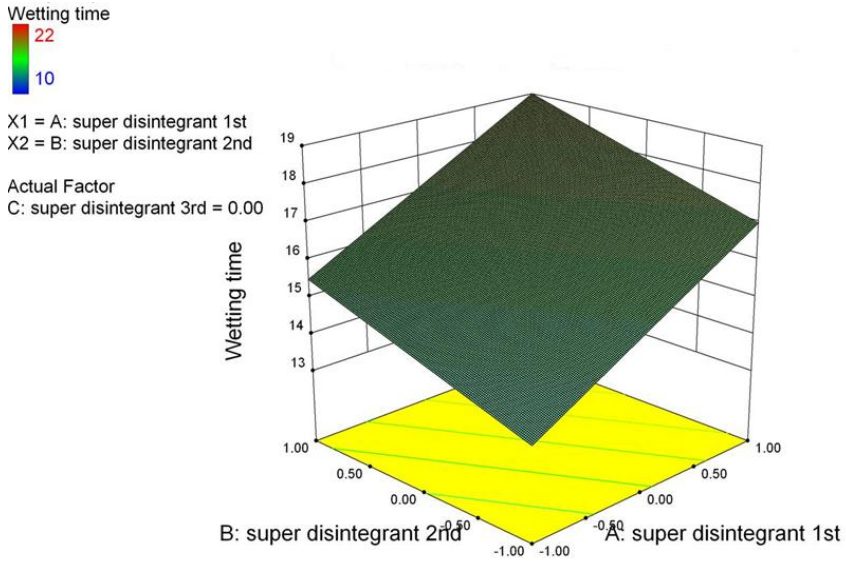

Figure 3: Wetting time as a product of superdisintegrants 1st and 2nd

2.12 In-vitro dispersion time

In vitro dispersion time is measure by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Tablets from each batch are randomly selected and *In -vitro* dispersion time was performed.[30]

2.13 Friability

It is measured of mechanical strength of tablets. Roche friabilator is used to determine by preweighed tablets are placed in the friabalator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes.[31-32] At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = loss in weight / Initial weight X 100

ANOVA for selected factorial model Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F
Model significant	2.050	3	6.833	7.81	0.0379
A-super disintegrant 1st	*8.000*	*1*	*8.000*	*9.14*	*0.0390*
B-super disintegrant 2nd	*8.000*	*1*	*8.000*	*9.14*	*0.0390*
C-super disintegrant 3rd	*4.500*	*1*	*4.500*	*5.14*	*0.0859*

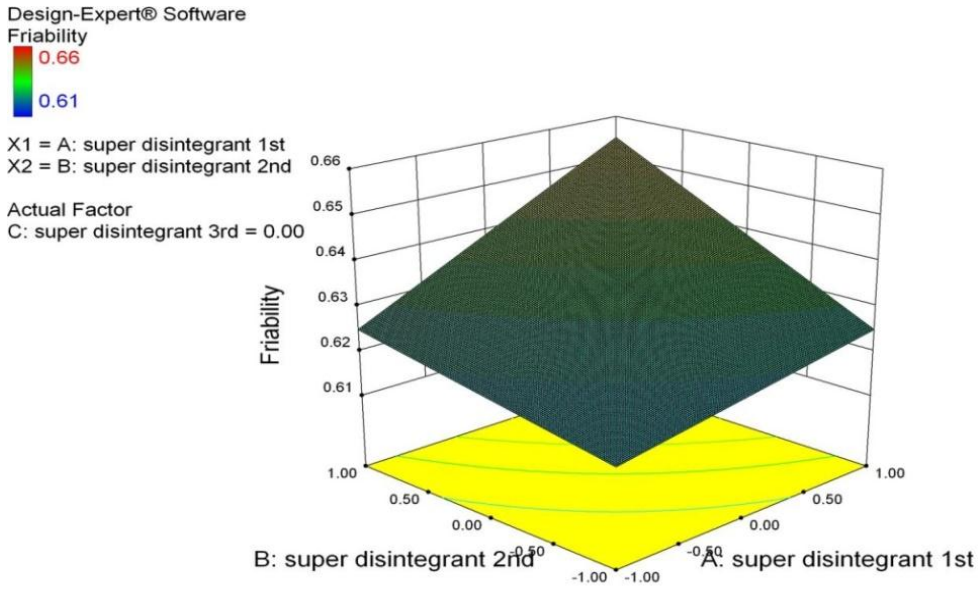

Figure 4: Friability as a product of Super Disintegrates 1st and 2nd

2.14 Tablet hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness.[33-35] Hardness of the tablet of each formulation is determined by using Pfizer/Monsanto Hardness tester.

ANOVA for selected factorial model Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F
Model significant	1.46	3	0.49	7.10	0.0443
A-super disintegrant 1st	*0.32*	*1*	*0.32*	*4.65*	*0.0972*
B-super disintegrant 2nd	*0.020*	*1*	*0.020*	*0.29*	*0.6183*
C-super disintegrant 3rd	*1.12*	*1*	*1.12*	*16.36*	*0.0155*

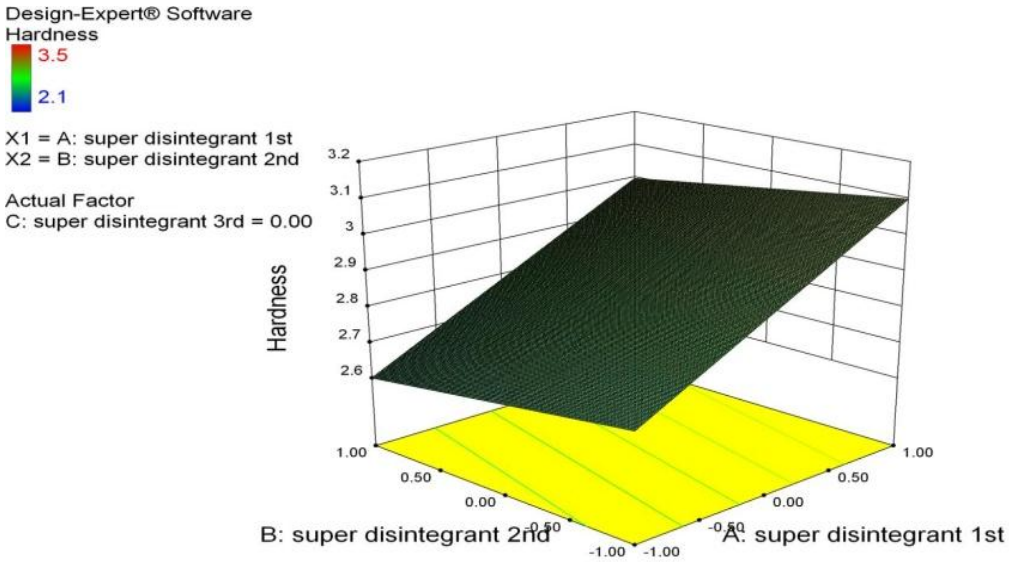

Figure 5: Hardness as a product of superdisintegrants 1st and 2nd

2.15 Content uniformity

Ten randomly selected tablets are weighed and average weight is calculated, the tablets are powdered in a glass mortar. The weight equivalent to tablet is weighed.[36] The weighed amount is dissolved in solvent system in separate volumetric flask using magnetic stirrer, the volume is adjusted with Sorenson's buffer pH 6.8 and the solution was filtered. An aliquot of these solution are diluted with Sorenson's buffer pH 6.8 in separate volumetric flasks in Lambert's-Beer's Range. The drug content in formulation is determined spectrophotometrically very easily.

216 In vitro dissolution studies

In-vitro dissolution studies for fabricated Fast Dissolving tablet is carried out by using USP XXIV paddle method at 50 rpm in 900 ml of Sorenson's buffer pH 6.8 as dissolution media, maintained at 37 ± 0.5^0C. 10 ml aliquots was withdrawn at the specified time intervals, filtered and assayed spectrophotometrically. An equal volume of fresh medium, which was pre-warmed at 37^0C is replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies are performed in triplicate.[37-38]

The various kinetic treatments are giving to the dissolution data. The in vitro dissolution data obtained were subjected to a zero order and first order kinetics, Higuchi model as well as Hixson Crowell Cube Root Law to understand the release profile and release mechanism.

ANOVA for selected factorial model Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F
Model significant	25.07	3	8.36	28.72	0.0036
A-super disintegrant 1st	*8.20*	*1*	*8.20*	*28.17*	*0.0061*
B-super disintegrant 2nd	*8.20*	*1*	*8.20*	*28.17*	*0.0061*
C-super disintegrant 3rd	*8.68*	*1*	*8.68*	*29.83*	*0.0055*

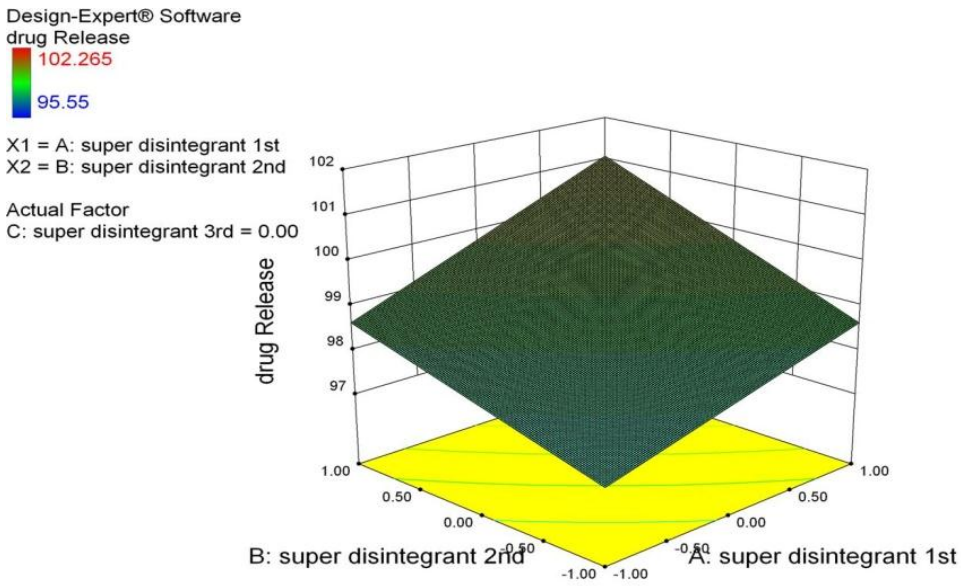

Figure 6: drug release as a product of superdisintegrants 1st and 2nd

3. RESULTS AND DISCUSSION

3.1Preformulation study

Determination of λ max in 0.1 N HCl media

Absorption maxima (λmax) was determined by scanning the drug X between 200 – 400 nm using UV spectrophotometer in 0.1 N HCl media, the Absorption maxima (λmax) of drug X was found to be at wavelength 258 nm corresponding to the value reported in literature.

3.2 Solubility study

The solubility of drug X was determined in different media the drug X was found to be practically insoluble in water and soluble in ethyl acetate, methanol, dimethyl formamide, dicloromethane and sparingly soluble in cyclohexane.[39]

3.3 Particle size determination

Particle size was determination using Malvern master size 2000. The 90% particle of drug X was less than 56.636 µm. Particle size and shape of the drug influence the flow and the mixing of powders and granules also may effect the Particle size can also be a factor in stability of tablt.

3.4 Powder flow properties

The flow properties of pure drug was studied as per observation, all the flow parameters like angle of repose, compressibility and hausner's ratio determine that the drug has passable flow. Therefore it was suggested to formulate the drug in a tablet dosage form with excipients and process in such a way to increases flowability.[40]

Good flow properties are a prerequisite for the successful manufacture of the tablet dosage form. At the Preformulation stage, data generated on low properties can be of great use in the development of the formulation. The data provided can give guidance on the selection of the excipients to use, the formulation type and the manufacturing process to use, for example, direct compression or granulation. It is important that once the habit and size distribution of the test compound have been determine, the flow properties are evaluated, if the intended dosage form is a solid dosage form.

3.5 Coating or encapsulation of superdisintegrants

Based on the feasibility 15% w/w concentration of dispersion (Solution of mannitol in water + Superdisintegrant (Polyplasdone XL10) was selected for spray drying process.

The spray dried blend of formulation F4 was found to have better flow property at inlet temperature (190-195^{0}C) and combination of polyplasdone XL10 & mannitol 25C (1:3).

Other parameters were kept constant with values -

- Outlet temperature : 85ºC
- Aspirator volume : 50
- Atomization : 1 Atm
- Pump rpm : 3 rpm

3.6 Evaluation of formulation parameters

Post compression parameters: The study included Average Weight, Thickness, Hardness, Disintegration Time, Wetting Time, Friability, In-vitro drug release studies as post compression parameters.

3.7 Post compression parameters

The average weight variation of tablet formulations F1, F2, F3, F4, F5 and F6 was found to be between 96 to 104 mg. The variation of weights was within the range of < 10% complying the USP pharmacopeia specification (Average weight of tablet 130 mg or less 10% weight variation). The hardness was found to be between 1.5 Kp to 2.0 Kp indicating satisfactory mechanical strength.

The thicknees was found to be between 2.65 mm to 2.75mm. The drug content uniformity was found to be between 99% to 107% it indicated uniform distribution of drug in the tablets for each formulation. The wetting time of tablet formulations F1, F2, F3, F4, F5, F6 were found to be 12, 14, 15, 5, 9, 11 sec respectively. The friability of tablet formulation F1,F2, F3, F4, F5, F6 were found to be 0.88%, 0.45%, 0.62%,0.29%, 0.42%, 0.35% respectively. The friability below 1% where indicated good mechanical resitence. The Disintegration time tablet formulation F1, F2, F3, F4, F5, F6 were found to be 8, 10, 12, 6, 8, 11sec respectively. The mouth feel property of F4 tablet formulation was found to be good, no grittiness, no chalkiness and smooth feel in tounge. All the formulation F1, F2, F3, F4, F5, F6 showed acceptable physicochemical properties like thickness, weight variation, hardness, drug content uniformity and *In vitro* drug release but F4 formulation showed best result in terms of disintegration time, friability, mouth feel property and wetting time due to better coating or encapsulation of superdisintegrant particle by mannitol solution in water and disintegration of tablet in particle level. So the F4 formulation was chosen as final optimized formulation.

3.8 *In vitro* drug release studies: The developed tablets were subjected to *in vitro* drug release studies in 0.1 N HCl for 45 min. The drug release studies carried out in dissolution test apparatus using 900 ml of dissolution medium, maintained at 37°C ± 0.5°C. Among all formulations, the drug release profile was all most same. 100% drug was released within 5 min from all formulations.

3.9 Stability study: The stability studies of final formulation was carried out for 2 months by packing the tablets in alu - alu pouch and keeping them in humidity chamber (40^0C/75% RH, 30^0C/75% RH, 25^0C/60% RH). The results indicated that formulation were stable including as supported data on content uniformity and dissolution profile so it indicated that the optimized formulation was stable.

4. SUMMARY AND CONCLUSION

The purpose of present study was to develop and characterize oral disintegrating tablets of anti-psychotic drug using spray drying technology. In this study, an attempt has been made to formulate oral disintegrating tablets, which are usefull for the patients suffering from panic disorder and cannot swallow solid oral dosage forms. The study involved Preformulation studies such as identification of drug, solubility study, particle size analysis and flow properties, Preparation of ODTS, Evaluation of developed formulations for various pre and post compression parameters. *In-vitro* drug release studies of prepared formulations. Stability studies of optimized formulation at different storage conditions i.e. 40 ± 2^0C/75 ± 5% RH, 30 ± 2^0C/75±5% and 25 ± 2^0C/60 ± 5% RH for 2 months.

A physicochemically stable oral disintegrating formulation of drug X was successfully designed. Amongst all trials, F4 (containing 80% co-processed excipient with an ratio of Polyplasdone XL10 & Mannitol 25^0C is 1:3; inlet temperature 190-195^0C) was found to be the most suitable oral disintegrating tablet formulation with regards to physical attributes such as disintegration time, wetting time, friability, mouth feel property and drug content uniformity found to be within Pharmacopoeial limits. Other physical attributes such as thickness, weight variation, hardness, drug content uniformity and *in vitro* drug release were found to be within Pharmacopoeial limits. Good storage stability as assessed by short term stability studies as per ICH guidelines. The study presents a new approach for the preparation of oral disintegrating tablets. The ODT´s exhibited characteristics of an ideal delivery system with an improved disintegrating and wetting time as well as create pleasant mouth feel. It is concluded that ODT´s prepared by spray drying technique can be used successfully for the treatment of psychotic disorder.

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