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Research Article

Formulation and Evaluation of Oral dispersible Tablet of Paroxetine Hydrochloride

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Abstract

Orodispersible tablets (ODTs) is a type of novel approach. It helps to increase user acceptance due to rapid disintegration, self-administration. ODT's like conventional tablets are solid dosage forms which contains super disintegrant, that helps to disintegrate the dosage form rapidly in the mouth within few seconds. The oro dispersible tablet of Paroxetine hydrochloride was prepared by using direct compression method and the tablet were formulated using various concentration of Kyron T-314 as disintegrating agent, PVP K-30 as binder, F melt Type C as diluent, Sodium Saccharin as sweetening agent, talc as lubricant and Aerosil as glident respectively. All the batches were prepared according to Factorial design. The prepared tablets were evaluated for various parameters like hardness, dissolution, friability, weight variation, disintegration time. The best batch was F5 whose disintegration time is minimum (26seconds) and better drug release profile. Orodispersible tablets of Paroxetine Hydrochloride were successfully formulated by which first pass metabolism could be avoided and faster onset of action could be achieved.

Keywords: Paroxetine hydrochloride, Orodispersible tablets, first pass metabolism, bioavailability, post menopause syndrome

INTRODUCTION

Menopause is the time in women's life when the menstruation stops forever and women is not able to bear young ones. This period is called as a climacteric. Menopause is many times defined by medical professionals as the condition when women have not any vaginal bleeding for about 12 months. Menopause is often observed between the age of 49 and 52 years.[1]

Post menopause is a period in women's life where their menstruation stops for 12 months or more, because of this their level of hormones will be constant. They will no longer be able to get pregnant or experience their menstruation cycles.[2] Depletion of ovarian follicles which are the primary source of estrogen represents primary ovarian failure. Majority of its symptoms are due to deficiency of estrogen but it can also occur due to aging so it becomes difficult to differentiate. The four major symptoms are lack of sleep, sexual dysfunction, hot flashes and mood changes. These are the most commonly observed in majority of cases.[3]

Oro dispersible dosage form is beneficial as it is easy to administer especially to the patients that have difficulty in swallowing such as pediatric, geriatric, mentally ill, disabled or uncooperative patients. It provides rapid dissolution of drug that may lead to it giving rapid onset of action. Bioavailability can be improved due to pre-gastric absorption which may further benefit as using reduced dosage form, improved clinical performance by reducing side effects. Highly convenient feature is that there is no need of water for swallowing especially for the patients that are travelling or the one who do not have immediate access to water. Drug gets absorbed in saliva as it passes through mouth, pharynx and esophagus till it reaches stomach; in such cases the bioavailability of drug increase. The psychology of "Bitter Pill" that occurs especially in pediatrics can be changed by the good mouth feel property of the ODTs. ODTs have the ability to provide the advantages of liquid medication in solid dosage form. This form can also avoid the first pass metabolism. It paves a way for new business opportunities such as: product differentiation, line extension and lifecycle management, exclusivity of product promotion and patent-life extension.[4]

MATERIALS AND METHOD

Direct Compression Technique is used for making the oral dispersible tablets of Paroxetine HCL. The total weight of tablets was 150mg and it was kept same in all formulated batches. Polacrillin Potassium (KYRON T-314) is used as disintegrating agent to facilitate tablet compression for greater hardness. As a Binding agent and suspending agent Polyvinyl pyrrolidone (PVP K-30) is used, it also increases the viscosity of melt type C which is a diluent composed of 55-70% D-mannitol, 10-25% MCC, 2-9% Xylitol, 5-13% Crospovidone, 2-9% dibasic calcium phosphate anhydrous and improves flow property and overall quality of drug. Aerosol is used as a glidant which has free flowing property and used as moisturized absorbent. Talc used as lubricant to improve flow property. Sodium saccharin which is a sweetening agent is 300-500 times sweet than sugar, heat stable and does not react chemically with other ingredients.

Direct Compression Method

For commercial preparation of oral dispersible tablet direct compression method is generally used. This process doesn't require the other granulating steps other than lubrication and compression and hence, it is a cost effective and effortless process in which the ingredients are jumbled well these tablets possess better strength and have rapid disintegration.[5]

All the powders were passed through sieve number 20. Required quantity of drug and various ingredients like disintegrating agent, binding agent, sweetening agent and diluent were mixed thoroughly. As a glident, Magnesium stearate and Aerosil were added and Talc was added as a lubricant. This Blend was compressed using by Rotary tablet machine.

Formulation of batches according to 3^2 full factorial designs

Table 1: Formulation of batches from F1 to F9

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
API (Paroxetine HCL)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Binder (PVPK-30)	1.5	1.5	1.5	2	2	2	2.5	2.5	2.5
Disintegrating agent (KyronT-314)	2	3	4	2	3	4	2	3	4
Sweetening agent (Sodium Saccharin)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Diluent (F-melt Type C)	131.5	130.5	129.5	131	130	129	129.5	128.5	127.5
Glident (Aerosil)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Lubricant (Talc)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150	150	150	150

Evaluation Parameters

The Oral dispersible tablets were evaluated for the following parameters:

Precompression parameters

Angle of repose:

It is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft.[6]

Bulk density:

Bulk density is the mass of a powder divided via the bulk volume. The density of a powder relies majorly upon primarily on particle length distribution, particle shape, and the tendency of the particles to stick to one another.[6]

Tapped density:

Tapped density is the ratio of powder mass to volume of powder after tapping for certain time period.[7] It is obtained by mechanically tapping a graduated cylinder containing the sample until volume change is observed. The tapping can be performed using different methods. The tapped density is calculated as mass divided by the final volume of the powder.

Carr's Compressibility index:

Carr's Index is measured using the values of bulk density and tapped density. Carr's index in an important parameter maintains weight uniformity.[8]

Hausner's ratio:

It indicates the flow properties of the powder. It is usually determined from the ratio between the tapped density (TD) and the bulk density (BD).[9]

Post Compression Parameters

The final tablets were evaluated for the following post compression parameters.

Weight variation:

The weight variation test was performed as per I.P. Twenty tablets were selected randomly from each batch and were weighed individually. And then average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. If no more than two tablets are outside the percentage limit than tablet passes the weight variation test.[10]

Hardness Test:

Monsanto hardness tester was used to determine the hardness of tablets; from each batch five tablets were

randomly selected. The mean values and standard deviation from each batch were calculated.[11]

Friability:

Roche Fraibilator was used to measure the friability of tablets. Twenty tablets have been initially weighed and transferred into Fraibilator. The Fraibilator become operated at 25 rpm for four minutes. The tablets were weighed again.[6]

Disintegration time (DT):

Disintegration test apparatus was used to find the in vitro disintegration time of the tablet. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube and apparatus was run using distilled water at 37 ± 2°C. And then complete disintegration of tablet with no palpable mass remaining in the apparatus was measured in seconds.[9]

Dissolution:

USP Dissolution rate Test Apparatus type-II was used to carried out dissolution study. In Dissolution apparatus 500ml of 6.8 phosphate buffers is used as a medium and the paddle was allowed to rotate 75 rpm. Temperature is maintained 37±0.5°C. 3 tablets were tested for dissolution.

RESULT AND DISCUSSION

Pre-formulation studies:

1. Organoleptic characteristics of Paroxetine HCL:

Table 2: Characteristics of Paroxetine HCL

Colour	White
Odour	Odourless
Taste	Slightly bitter

2. Melting point characteristics:

Veego melting point apparatus was used to measure the melting point of the drug. A minute amount of drug was taken in capillary which was closed from one end and placed in the apparatus and the temperature at which the drug starts melting was noted.

3. UV spectroscopic analysis of Paroxetine HCL:

Preparation of calibration curve of Paroxetine HCL using suitable solvent:

Phosphate buffer 6.8

Stock solution

Aliquot: From the stock solution 1mL of sample was taken into 10mL of volumetric flask and volume was made up by adding 9mL of phosphate buffer and this gave 100mcg/mL of solution. Serial dilution was carried out for 1mL, 2mL, 3mL, 4ml, 5ml, 6mL, 7mL, and 8mL samples and diluted up to 10ml to get concentration of 10mcg/mL, 20mcg/mL, 30mcg/mL, 40mcg/mL, 50mcg/mL, 60mcg/mL, 70mcg/mL and 80mcg/mL respectively.

Determination of UV absorption maxima:

From the above prepared aliquot, the middle concentration (50mcg/mL) was taken and scanned for absorbance between 200-400nm using UV- visible spectroscopy. Paroxetine exhibits UV absorption maxima at 293nm.

FTIR study

FTIR study is done to check the compatibility of Paroxetine HCL with their excipients; FTIR Spectra of the formulation along with Excipients were obtained. The method used was Potassium bromide (KBr) Pellet. The samples were rigorously blended with dry powdered KBr crystals. The functional groups were identified by FTIR spectroscopy of pure Paroxetine. The major group of Paroxetine HCL was found to be stretching of amine group, carbonyl group incompatibility with their excipients.

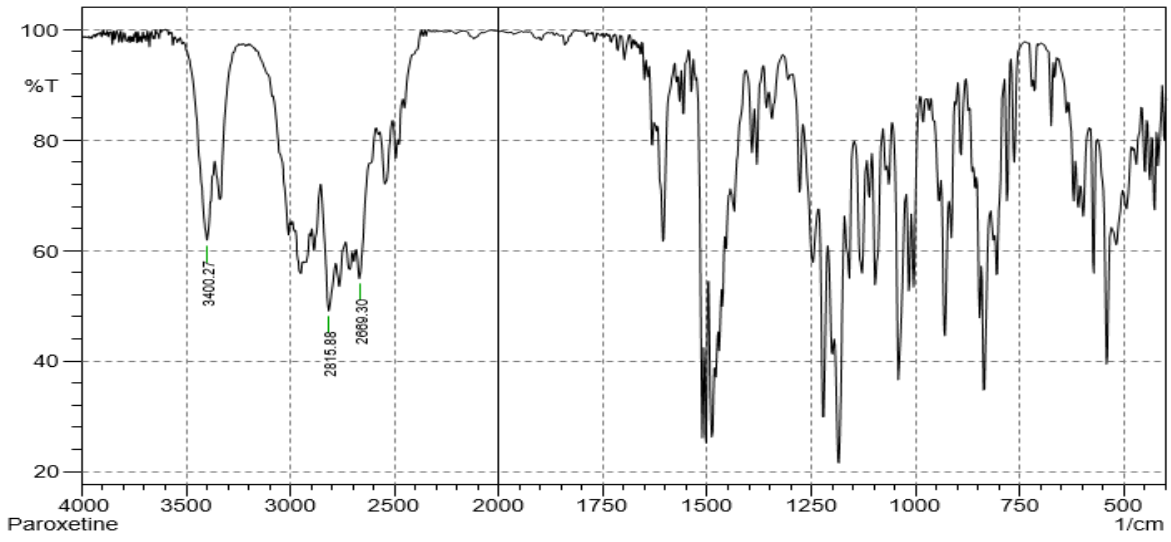

Figure 1: FTIR of Paroxetine HCL

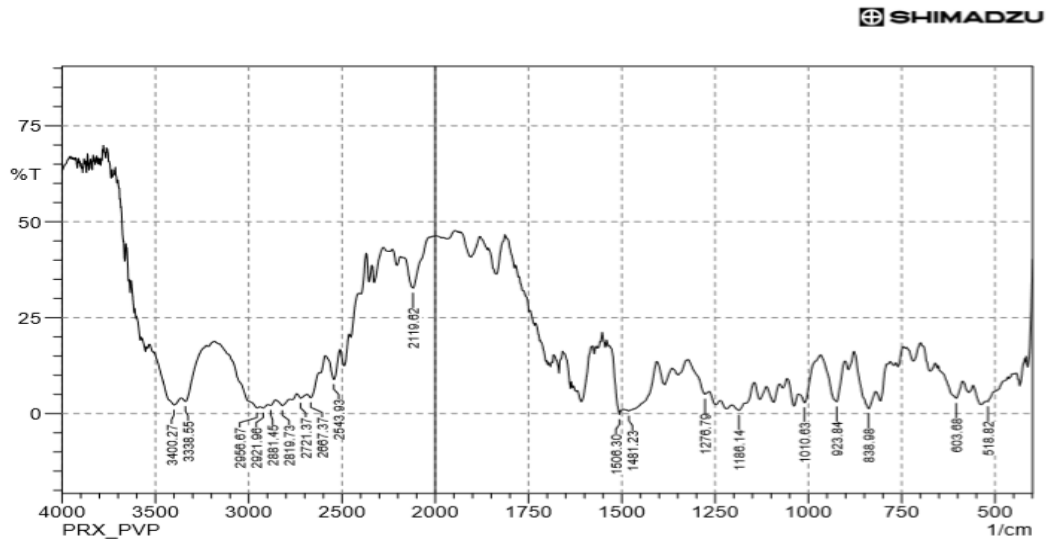

Figure 2: FTIR of Paroxetine HCL + PVP K30

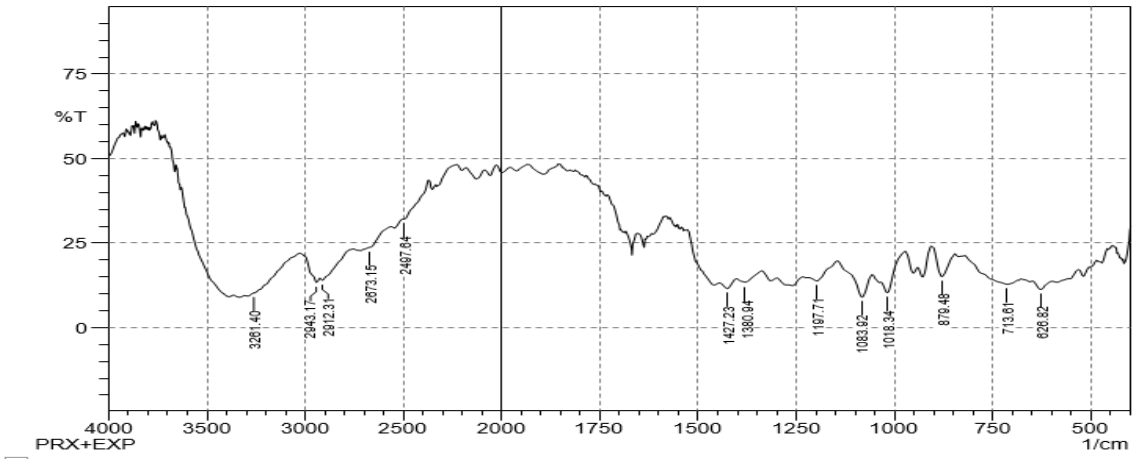

Figure 3: FTIR of Paroxetine HCL + Excipients

DSC study

DSC is used for the compound characterization and purity of drug is checked via its melting point. It is also used to check if there is any interaction between drug and excipients. The melting point range of Paroxetine HCL as shown in figure5.6 was found to be in range of 118.15°-130.44°C which is comparable with the reported range of drug (120°-138°). Change in the peak can be observed if there is any interaction between the drug and excipients but the result figure does not show any change in the peak of Paroxetine HCL along with the excipients, which concludes that there is no incompatibility with the excipients added.

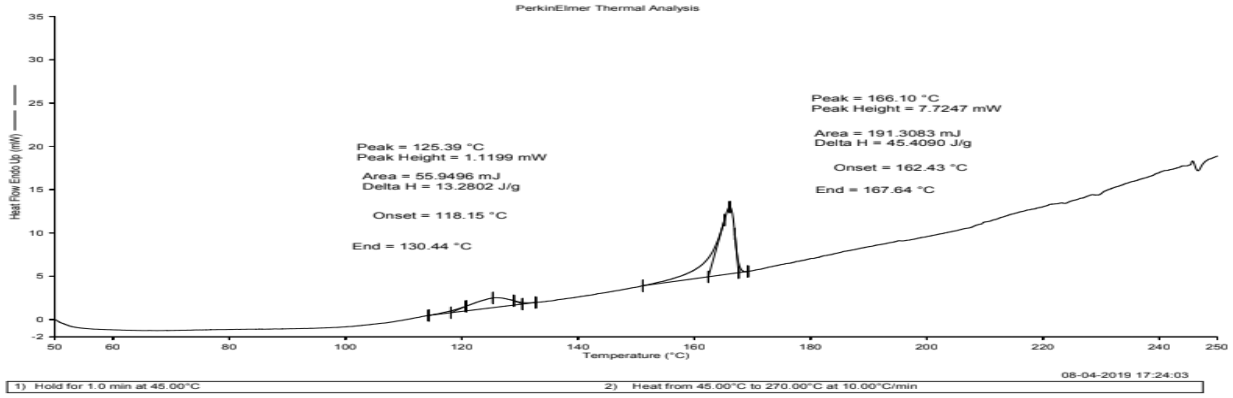

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Figure 4: DSC of Paroxetine HCL

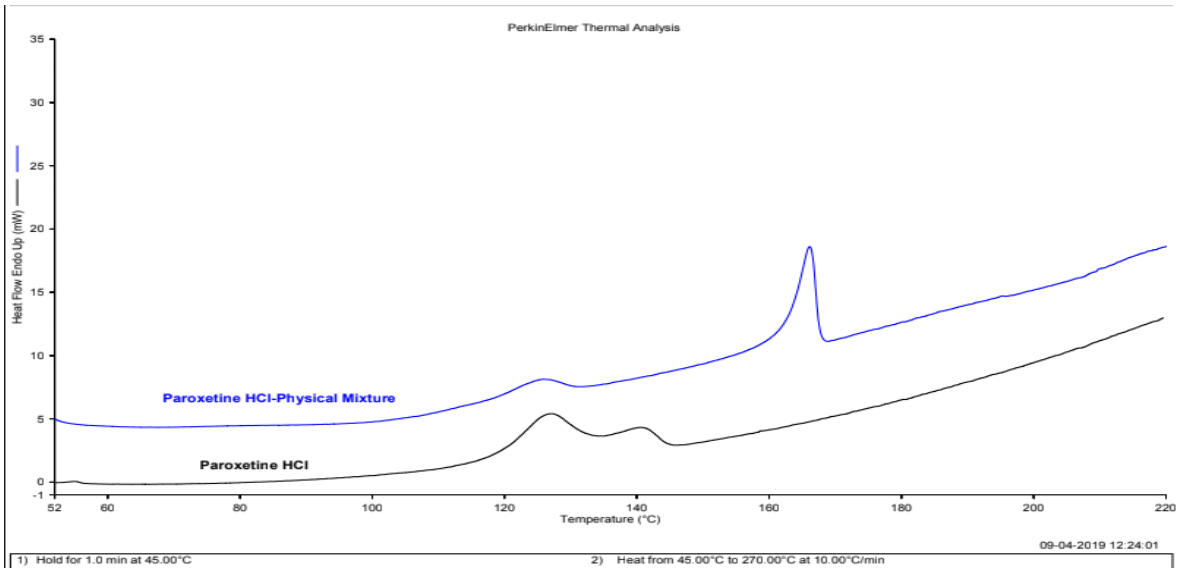

Figure 5: DSC of Paroxetine HCL + Excipients

Result of Pre and Post Compression Batches:

Pre compression of F1 to F9

Table 3: Pre-compression result of F1 to F9 batches

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of Repose	23.59	24.13	23.98	25.64	22.91	23.67	25.21	22.31	23.56
Hausner's ratio	1.13	1.10	1.01	1.15	1.07	1.17	1.11	1.03	1.18
Carr's Index	12.65	17.34	11.72	15.21	12.66	10.99	17.01	14.67	13.76

Post compression of F1 TO F9

Table 4: Post compression results of F1 to F9 Batches

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm2)	3.45	3.06	3.23	3.89	4.20	3.98	4.00	4.90	5.21
Thickness (mm)	3.56 ±0.02	3.12 ±0.03	3.02 ±0.02	3.27 ±0.01	3.20 ±0.02	3.07 ±0.03	3.43 ±0.02	3.19 ±0.01	3.64 ±0.02
Diameter (mm)	6.09± 0.02	6.05 ±0.03	6.04± 0.01	6.07± 0.02	6.02± 0.03	6.03± 0.01	6.04± 0.02	6.02± 0.03	6.00± 0.02
Disintegration time(sec)	35±2	29±1	32±1	27±3	26±3	33±1	34±2	29±1	28±1
Drug release at 15min	87.64 ±0.23	85.45 ±0.20	89.78 ±0.24	90.43 ±0.27	92.56 ±0.20	89.90 ±0.23	90.89 ±0.25	88.12 ±0.22	88.90 ±0.20
Wetting time(sec)	18±3	17±2	21±2	17±1	14±1	20±3	15±2	16±2	15±1
Weight variation	157±2	154±3	149±1	149±1	149±3	152±1	148±2	143±3	146±3
Friability	0.55	0.69	0.78	0.78	0.52	0.63	0.77	0.87	0.64

The Design Expert 13 was used to identify statistical analysis of the design batches by multiple linear regression analysis. The coefficient showing p value >s0.05 were removed from the regression to generate reduced model. This model is used for calculations of unused materials or for drawing contour plots using design expert. The conclusion of results of regression analysis full and refined models ($p<0.05$) for disintegration time in seconds (Y1) and % drug release at 15 minutes (Y2). The polynomial equations are used to draw or identify conclusions after considering the results of

coefficient and the mathematical sign it has, i.e., positive or negative. Those coefficients were recorded to be insignificant at p-value more than0.05; their values were omitted from the full model to generate the reduced model. The high values of correlation coefficient for Y1 and Y2 indicate a good fit.

Factorial Equation for Disintegration time (Y1)

Y1=10.83- 7.87(X1) -4.50(X2) +3.81(X1)(X2) +8.50(X1)^2 +18.33(X2)^2

Factorial Equation for % Drug release at 9 minutes (Y2)

Y2=96.36- 0.7185(X1) +2.00(X2) -2.24(X1)(X2) -1.61(X1)^2 -7.98(X2)^2

Effect of X1 and X2 on % Drug release:

The polynomial equations can be used to calculate conclusions after considering the magnitude of coefficient and the mathematical sign it shows. The coefficient obtained shows that coefficient b1, b2 were negative and b12, b22 and b12 were positive. The negative sign for b1, b2 indicated that Kyron T-314 and Pvp K-30 were significantly affecting % drug release in opposite manner. After the optimized concentration excipients (Kyron T-314 and Pvp K 30) were started to show negative effects. The coefficient indicated that X1 has more effective than X2 on % drug release. The response surface plot and contour plot of effect of Kyron T-314 and Pvp K 30 on % drug release are shown in below Figures.

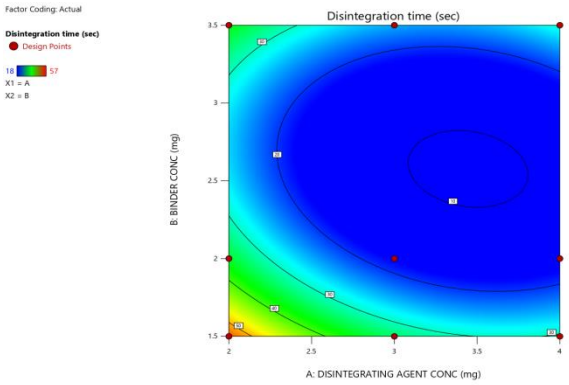

Figure 6: Counter plot of response Y1

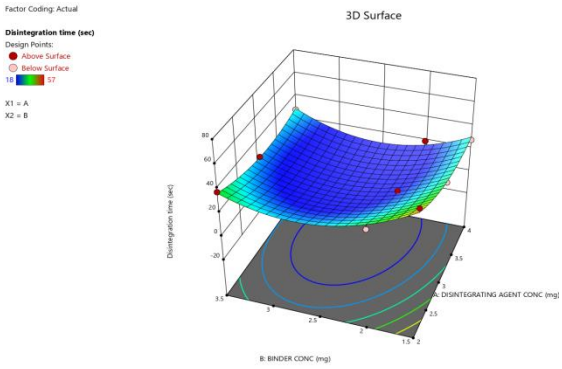

Figure 7: 3D plot of response Y1

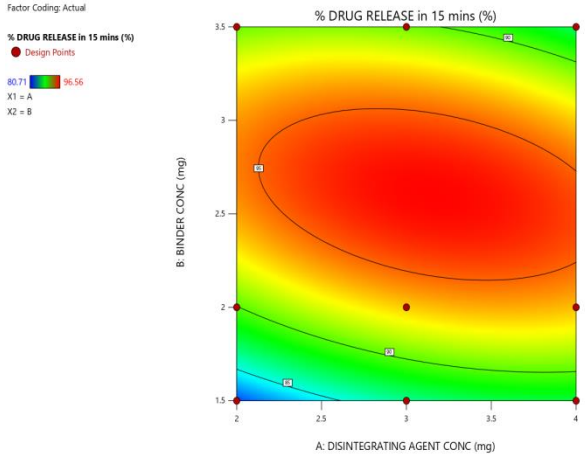

Figure 8: Counter plot of response Y2

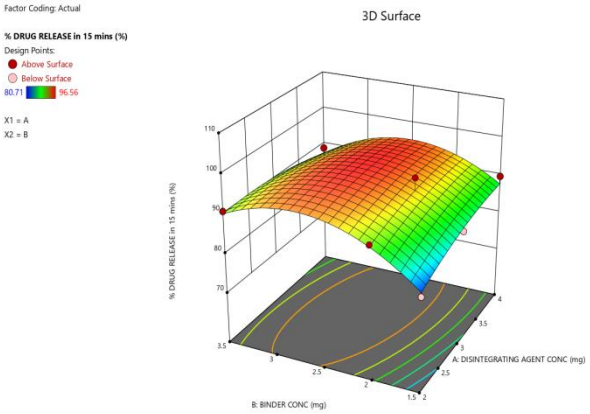

Figure 9: 3D plot of response Y2

SUMMARY AND CONCLUSION:

In the present study, oral dispersible tablet of Paroxetine HCL was formulated. Paroxetine HCL belongs to class of selective serotonin reuptake inhibitor and it is used for treating depression but its lower dose (7.5mg) is used in treatment of post-menopausal symptoms. The marketed preparation of Paroxetine HCL shows slow onset of action and 50% of the drug undergoes first pass metabolism. Thus, to achieve fast onset of action and overcome the first pass metabolism oral dispersible tablet of Paroxetine HCL was formulated. Kyron T-314 and PVP K-30 are used as a disintegrating agent and binder at minimum to maximum quantity which gives better disintegration time and binding property was studied. Initially study gives the report that as we increase the concentration of disintegrant and binder, the disintegrating time and the binding property also increases. The batch F5 can be considered as optimized batch as the disintegration time is minimum (26seconds). The optimized formulation batch F5 showed better drug release profile with other formulations. From the present study carried out on Paroxetine HCL oral dispersible tablet using by direct compression method the following conclusion can be drawn. The total weight of F5 bath was 150mg containing Paroxetine HCL-7.5mg, PVP K-30 2mg, Kyron T-314 3mg, Sodium saccharine 4.5mg, F-melt Type C 130mg, Aerosil 1.5mg and Talc 1.5mg. Pre compression parameters such as Angle of repose, Carr's index, Hausner's ratio and Post compression parameters such as Hardness, Thickness, Friability, Weight variation, Disintegration time, wetting time etc. were in proper range in this particular batch (F5). Our objective to cost effective oral dispersible tablet by direct compression quickly disperse in oral cavity and it definitely gives the fast release action for its post-

menopausal activity. Fast disintegration of tablet formulated in this investigation may help in administration of Paroxetine HCL in a palatable form without using water. Formulation F5 gives the quick disintegration and better drug release. Hence it can be concluded that the formulation F5 is a stable and effective for quick action and it is alternative to the conventional tablet.

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