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FORMULATION, DEVELOPEMNT AND EVALUATION OF ZIPRASIDONE HYDROCHLORIDE CAPSULES BY DRY GRANULATION METHOD

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ABSTRACT

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit.[1] Variable gastric emptying gives non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the required site. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed.[2] The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine). Floating systems are one of the important categories of drug delivery systems with gastric retentive behaviour.[3]

Capsules are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or ‘shell.’ The shells are usually formed from gelatin; however, they also may be made from starch or other suitable substances. Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert

ingredients are enclosed in a small shell or container usually made of gelatin. The medication may be a powder, a liquid or a semisolid mass. Capsules are usually intended to be administered orally by swallowing them whole. Occasionally, capsules may be administered rectally or vaginally.[4]

KEYWORDS: *Dry granulation, direct compression, Roller compactor.*

INTRODUCTION

Ziprasidone, commercially available as Geodon capsules, is an atypical antipsychotic used in the treatment of schizophrenia and bipolar disorder. It is a BCS Class II drug that shows up to a 2-fold increase in absorption in the presence of food. Because compliance is a major issue in this patient population, we developed and characterized solubilized formulations of ziprasidone in an effort to improve absorption in the fasted state, thereby resulting in a reduced food effect.[5]

This formulation increase solubility and dissolution rate of ziprasidone hydrochloride. For increasing the solubility of drug solubility study is carried out without SLS, with 1%SLS, with 2% SLS in different dissolution media. The pre-formulation study carried out like Identification test, water content, particle size, granules parameter(bulk density ,compressibility index), drug-excipient compatibility studies are carried out up to one month period at $25^0C \pm 2^0$ C /60%RH ± 5% RH (2Weeks) and (1 month), 40°C ± 2 ^{0}C/75%RH ± 5% RH (2Weeks) and (1 month) and $60^0C \pm 2\ ^0C$ for open condition. The first trail was carried out by direct compression method but because of improper flow trail is taken with dry compression with roller compaction. Trail taken as per innovator formula. Formula optimization and process optimization batches carried out and select the design space for parameters by ANOVA software.[6]

Capsules were evaluated based on different parameters such as thickness, weight variation, content uniformity, disintegration test, assay, water content, impurity study, in-vitro dissolution studies, content of active ingredient and IR studies. The physico-chemical properties of the finished product complied with the specifications. *In vitro* release from the formulation was studied as per the USP XXIII dissolution procedure.[7]

Fig.No.1 Capsule sizes.

Sizes

• 000 (largest) > 00 > 0 > 1 > 2 > 3 > 4 > 5

The compaction of powder by use of pressure roll can also be accomplished by a machine called chilsonator. Unliketablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled to produce granules.in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations.[8]

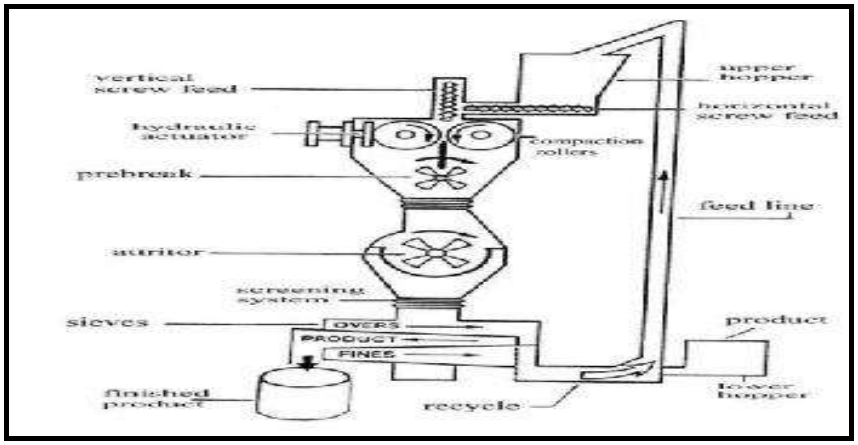

Fig No. 2: Chilsonator.

MATERIALS AND METHOD

Ziprasidone Hydrochloride was received as gift sample from Ajanta Pharma Ltd Mumbai, Lactose Monohydrate, Lactose anhydrous, magnesium stearate, Colloidal Anhydrous Silica, Pregelatinised starch, Povidone, Polysorbate 80 were procured as gift samples from Signet, Dow chemical and Merck All other reagents and chemicals used of analytical grade.

EXPERIMENTAL

The objective of formulation development was arrive at a stable & effective formula for Ziprasidone Hydrochoride Capsule with the similar characteristics of innovator product. Ziprasidone Hydrochloride is cohesive and displays poor flowability as evidenced by the compressibility index, Hausner ratio. Poor material flow may produce tablets with high weight and content variability due to an uneven distribution of the drug substance in the blend, uneven bulk density and eventually, uneven filling of capsules. Initial trial was taken by direct compression was according to innovator formula but blend had poor flow, capsules were not filled properly. Further trials were taken by Dry granulation method by roller compaction which was according to Innovator and its composition. For dry granulation by roller compaction, the powder particles of drug substance and fillers are aggregated under high pressure to form a ribbon and then broken down to produce granules by milling before filling. Due to the problem of flow properties of blend, the formulation could not make satisfactory. So the Dry granulation shifted to wet granulation by Fluidized bed processer and achieved optimum flow properties. The formulations were optimized by applying 2^2 factorial designs and process was optimized 2^{3-1} fractional factorial designs. The stability study of best optimized formulation was done.[9]

Direct Compression Method

a) Trial 1: ZHC1.

Batch size -1000 tablets.

Table no. 1: Development Trail 1 formula.

Sr. No	Ingredients	Specification	Quantity per unit (mg)	Quantity for batch (g)
Active Pharmaceutical Ingredient				
1	Ziprasidone Hydrochloride	USP	22.64	22.64
Excipients				
2	Lactose Anhydrous (SuperTab 21 AN)	USP-NF	39.235	39.235
3	Pregelatinized Starch (Lycatab PGS)	USP-NF	12.75	12.75
4	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
5	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
Therotical weight of Lubricated blend			75	75
EHG Capsule				
6	E.H.G Capsule size ‘5’ Blue opaque/White opaque, ‘ap’ logo & ‘ZP 20’ on cap & body respectively	IH	1 No.	1000 No.

Observation: Blend had very poor flow. Capsules were not filled properly and completely.

Conclusion: Next trial was planned to improve BD and flow properties. Trial taken with Roller Compaction method.

By Dry granulation method.

a. Trial 2: ZHC2.

Batch size -1000 tablets.

Table no. 2 Development Trail 2 formula.

Sr. No.	Ingredients	Specification	Quantity per unit (mg)	Quantity for batch (g)
Active Pharmaceutical Ingredient				
1	Ziprasidone Hydrochloride	USP	22.64	22.64
Excipients				
2	Lactose Anhydrous (SuperTab 21 AN)	USP-NF	39.235	39.235
3	Pregelatinized Starch (Lycatab PGS)	USP-NF	12.75	12.75
4	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
5	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
Theoretical weight of Lubricated blend			75	75
EHG Capsule				
6	E.H.G Capsule size '5' Blue opaque/White opaque, 'ap' logo & 'ZP 20' on cap & body respectively	IH	1 No.	1000 No.

Observation: All flow and related parameters were improved.BD and TD was improved from 0.2 to 0.4-0.5 and 0.4 to 0.7-0.8.

Conclusion: Next trial planned with increasing Roller pressure and lubricating two times.

b. Trial 3: ZHC3.

Batch size -1000 tablets.

This batch was taken by increasing roller pressure and lubricating two times.

Parameter of roller compaction: Roller pressure-3T, Roller speed-6 rpm.

Table no. 3: Development Trial 3 formula.

Sr. No.	Ingredients	Specification	Quantity per unit (mg)	Quantity for batch (g)
Active Pharmaceutical Ingredient				
1	Ziprasidone Hydrochloride	USP	22.64	22.64
Excipients				
2	Lactose Anhydrous (SuperTab 21 AN)	USP-NF	39.235	39.235
3	Pregelatinized Starch (Lycatab PGS)	USP-NF	12.75	12.75
4	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
5	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
Therotical weight of Lubricated blend			75	75
EHG Capsule				
6	E.H.G Capsule size '5' Blue opaque/White opaque, 'ap' logo & 'ZP 20' on cap & body respectively	IH	1 No.	1000 No.

Observation: Flakes formed were to hard .passing these through 20 mesh was not smooth.

Conclusion: Next trial was planned with different compaction parameter.

c. Trial 4: ZHC4

Batch size -1000 tablets

Batch taken with Roller pressure 4T Roller pressure, Roller speed 6 rpm.

Table no. 4: Development Trial 4 formula.

Sr. No.	Ingredients	Specification	Quantity per unit (mg)	Quantity for batch (g)
Active Pharmaceutical Ingredient				
1	Ziprasidone Hydrochloride	USP	22.64	22.64
Excipients				
2	Lactose Anhydrous (SuperTab 21 AN)	USP-NF	39.235	39.235
3	Pregelatinized Starch (Lycatab PGS)	USP-NF	12.75	12.75
4	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
5	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
Therotical weight of Lubricated blend			75	75
EHG Capsule				
6	E.H.G Capsule size '5' Blue opaque/White opaque, 'ap' logo & 'ZP 20' on cap & body respectively	IH	1 No.	1000 No.

Observation: Pressing required for capsule filling.

Conclusion: Next reproducible trail taken based on trial 4.

d. Trial 5: ZHC5.

Batch size -1000 tablets.

Batch taken with Roller pressure 4T Roller pressure, Roller speed 6 rpm. Capsules filled with automated capsule filling machine.

Table no. 5 Development Trial 5 formula.

Sr. No.	Ingredients	Specification	Quantity per unit (mg)	Quantity for batch (g)
Active Pharmaceutical Ingredient				
1	Ziprasidone Hydrochloride	USP	22.64	22.64
Excipients				
2	Lactose Anhydrous (SuperTab 21 AN)	USP-NF	39.235	39.235
3	Pregelatinized Starch (Lycatab PGS)	USP-NF	12.75	12.75
4	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
5	Magnesium Stearate (Tablube)	USP-NF	0.1875	0.1875
Theoretical weight of Lubricated blend			75	75
EHG Capsule				
6	E.H.G Capsule size '5' Blue opaque/White opaque, 'ap' logo & 'ZP 20' on cap & body respectively	IH	1 No.	1000 No.

Observation: required weight achieved and capsules were filled properly by automated capsule filling machine.

Conclusion: It is an optimized batch .based on this formulation the process and formula optimization to be carried out.

Manufacturing process: - Batch – ZHC1 to ZHC5

1.1.1. Dispensing of Raw Materials.

1) All the ingredients were weighed accurately including the Ziprasidone Hydrochloride.

2) Weighing was done in separate poly bags.

1.1.2. Manufacturing Process.

1.1.2.1 Sifting, Pre- compaction mixing, and Compaction.

1) Co-sifted Ziprasidone Hydrochloride, Lactose Anhydrous (SuperTab 21 AN) and Pregelatinized Starch (Lycatab PGS) through # 30 S.S. sieve.
2) Magnesium Stearate (Tablube) sifted through # 60 S.S. sieve
3) Transfered the co-sifted materials of step 1 into blender.
4) Added sifted Magnesium stearate of step 2 into blender
5) Mixed the materials for 10 minutes at 10 rpm.
6) Unloaded the blend from the Blender.
7) Loaded the blend of step 6 into hopper of roller compactor. The blend was compacted by maintaining the roller speed 4 to 10 rpm, roller pressure 2 to 8 Tones (12 to 100 Bar), augar speed 5 to 30 rpm, and roller direction forward and sifted through #30 to separate powder adhered to compacts. The compacted material collected into double polyethylene lined container.

1.1.2.2 Milling and Sifting

1. Transferred the compacted material from step 7 to mill.
2. Milled the material using 1.5 mm screen at slow speed.
3. Sifted milled material through #30 SS sieve.

1.1.2.3. Lubrication

4. Loaded the material of step 2.2 into Blender.
5. Weighed and sifted the remaining quantity of Magnesium stearate through #60 S.S. sieve
6. Co-sifted granules of step 2.2 and sifted Magnesium Stearate (Tablube) of step 2.3.2 through #30 SS sieve and transferred in to the Blender and mixed the materials for 5 minutes at 10 rpm.
7. Weighed and recorded the net weight of the lubricated blend.
8. Capsule filling was done by manual capsule filling machine.

1.2 Formula optimization by Roller Compaction method

1.2.1 Factorial designs[30]

It is well known that traditional experimentation involves a good soal of efforts and time especially when complex formulation are to be developed. It is desirable to develop an expectable pharmaceutical formulation in the shortest period of time using minimum number of man-power and raw materials. In addition to the art of formulation, factorial design is an

efficient method of indicating the relative significance of a number of variables and their interaction. Factorial design approach shows interaction between factors that a 'one factor at a time' model cannot reveal.

1.2.2 Two Level Factorial Designs[30]

A two-level factorial design is an experimental design in which data is collected for all possible combinations of the two factors by considering two levels of each. Hence the two level factorial design was applied for optimization experiments. The table 5.8 shows two factors such as Pre-gelatinized starch and Magnesium stearate (Binding agent and Lubricating agent) in low and high levels of concentration. The table 5.9 shows the lowest concentration for Pre-gelatinized starch and Magnesium stearate was 7.0% and 0.25%, respectively, whereas the highest concentration for the same agents was 27% and 0.75%, respectively.

Table 6: Two factors for DOE.

Levels		
	-1	**+1**
Factor 1	Pre-gelatinized starch	Pre-gelatinized starch
Factor 2	Magnesium stearate	Magnesium stearate

Table 7: Two factors with, low and high concentration for DOE.

Levels		
	-1	**+1**
Pregelatinised starch	7	27
Magnesium stearate	0.25	0.75

In factorial design the Anova software has given responses for two factors considering one centre point. Given responses includes main effect plots and some specified set of two factor interactions plots. The table 5.10 shows five experiments considering centre point. In case of Response Surface Method (RSM) center point was not considered. Hence the software has given four experiments which include the contour plots and surface plots.

Table 8: Factorial design batches with center point.

Batch No	**Pre-gelatinized starch**	**Magnesium stearate**
ZHC6	17	0.5
ZHC7	27	0.75
ZHC8	27	0.25
ZHC9	7	0.75
ZHC10	7	0.25

1.2.3 Optimization Batches by Roller compaction

Total 5 optimization batches taken place including one center point.

Table no 9: Optimization batches formula (mg/ tab).

Sr. no.	Ingredients	ZHC6	ZHC7	ZHC8	ZHC9	ZHC10
		mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
	Intra granular					
1	Ziprasidone Hydrochloride	22.64	22.64	22.64	22.64	22.64
2	Lactose Anhydrous	39.23	31.50	31.50	46.51	46.51
3	Pregelatinized starch	12.75	20.29	20.66	5.29	5.6
	Lubrication					
4	Magnesium Stearate	0.38	0.563	0.188	0.563	0.188
	Total	**75**	**75**	**75**	**75**	**75**

1.2.4 Process Optimization by Roller compaction Method:

For Process optimization 2^{3-1} Fractional factorial applied with considering following parameters.

i. Pre-lubrication time(mixing)
ii. Roller pressure
iii. Screen used
iv. Lubrication time

The table 5.10 shows 9 experiments considering center point. In case of Response Surface Method (RSM) center point was not considered. Hence the software has given four experiments which include the contour plots and surface plots.

Table no. 10: Process variables for process optimization batches.

Batches	Process variables			
	Pre-lubrication time	Roller pressure	Screen used	Lubrication time
ZHC11	10	4	1.5	5
ZHC12	5	2	1	3
ZHC13	5	6	1	7
ZHC14	15	6	1	3
ZHC15	15	2	2	3
ZHC16	15	6	2	7
ZHC17	15	2	1	7
ZHC18	5	2	2	7
ZHC19	5	6	2	3

RESULT AND DISCUSSION

Evaluation of Development batches.

1.1 Capsules parameter.

Table No. 11 Capsule parameter of Trial 5.

Sr. No	Parameter	Result
1	Description	Blue opaque/ white opaque hard gelatin capsule of size '5' with ap logo on cap and 'ZP 20' on body in black ink containing white to slightly pink colored powder .
2	Average weight of filled capsule	105.02 mg
3	Capsule lock length	11.58 mm
4	Disintegration Time	6 min 20 sec
5	Water content	3.16% w/w
6	Assay	98.6 %
7	Content Uniformity	97.5%

- **Weight Variation**

In weight variation test, the Pharmacopoeial limit for percent of deviation for capsules weighing less than 300 mg is not more than 10%. The average percent deviation of all capsules was found to be within the limit and hence all formulation passes the weight variation test.

- **Capsule lock length**

Capsule lock length of capsules was found to be uniform among all formulations and range d from 11.00 to 11.80 mm**.**

- **Content Uniformity**

The drug content was found to be uniform among all formulation and ranged from 85.00% to 115.00%.

- **Assay**

Assay of all the formulations was found to be between 95-105% and assay of ZHC5 optimized batch was found to be 98.6%.

1.2 Particle size analysis.

Table No 12: Particle size analysis of Trial 5.

Sieve no.	Empty wt.	Wt. with blend	Wt. of blend	% Retained	Cumulative
30	384	384	0	0	0
40	357.5	358	0.5	1.92	1.92
60	350.5	357.5	7	26.92	28.85
80	343	349.5	6.5	25.00	53.85
100	328	331.5	3.5	13.46	67.31
Pan	549	557.5	8.5	32.69	100.00
			26 g	100	

1.4.1 Dissolution results.

Compilation of development batches dissolution.

Dissolution media: Sodium Phosphate buffer pH 7.5% with 2 % SLS (OGD), 75 rpm, 900 ml, USP-II.

Table No 13: Compilation of Dissolution result of development batches.

Time	Reference	ZHC1	ZHC2	ZHC3	ZHC4	ZHC5
0	0	0	0	0	0	0
5	24.1	35.6	21.9	37.6	30.1	27.5
10	58.4	60.5	42.6	66.1	56	58.1
15	71.4	72.7	54.9	76	69.2	71.1
20	80.2	80.3	62.8	83.2	77.2	76.3
30	85.9	85.3	72.4	86.2	84.9	82
45	91.9	89.1	79.9	89.5	89.2	86.5
60	95.4	91.1	84.2	90.9	91.8	88.9
F1		**14.47**	**18.79**	**7.65**	**4.21**	**4.18**
F2		**64.87**	**42.83**	**58.14**	**73.34**	**72.25**

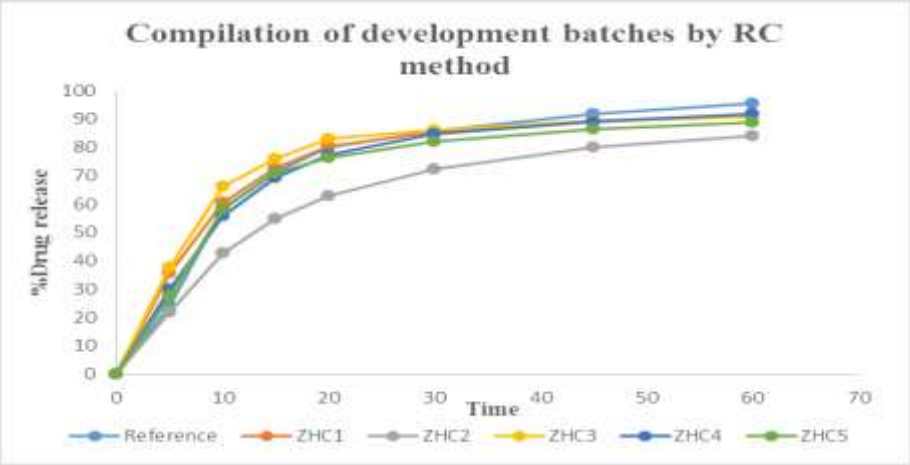

Fig. No. 3: Compilation of dissolution data of development batches.

6.4. Compilation of dissolution profile of Process Optimization batches.

Table No 14: Dissolution data compilation of Process optimization batches.

Time	Reference	ZHC11	ZHC12	ZHC13	ZHC14	ZHC15	ZHC16	ZHC17	ZHC18	ZHC19
0	0	0	0	0	0	0	0	0	0	
5	24.1	26.4	34.6	37.6	48.1	31	34.6	28.6	26.8	26.1
10	58.4	57.2	59.2	65.4	75.6	59.6	59.2	60.7	54.6	54.2
15	71.4	69.8	69.2	77	81.1	70.4	69.5	73.7	67.8	66.7
20	80.2	76	75.3	83.1	84.2	75.6	75.3	80	75.2	73.6
30	85.9	81.9	80.6	88.8	87.3	81.6	80.6	86.2	82.5	80.8
45	91.9	86.3	84.9	92.7	91.6	86.2	84.9	90.2	88	85.3
60	95.4	89	87.1	94.5	93.2	88.6	87.1	93.2	91	87.5
F1		**5**	**7.63**	**6.04**	**11.59**	**6.04**	**7.63**	**2.64**	**5.32**	**7.35**
F2		**68.8**	**59.56**	**64.99**	**46.16**	**65.01**	**59.63**	**79.8**	**69.66**	**62.19**

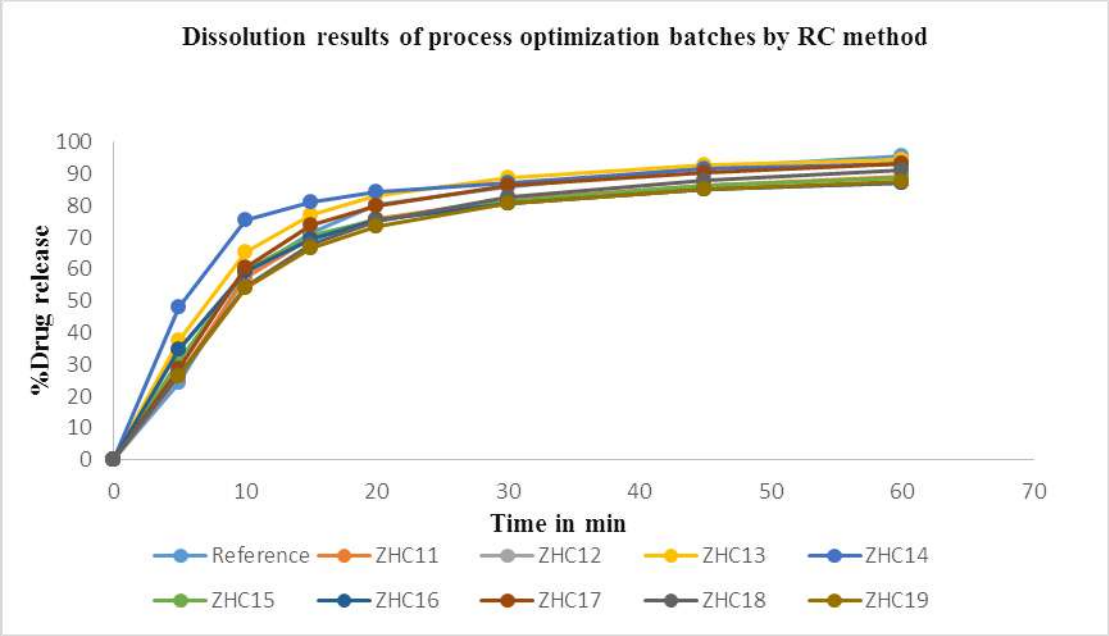

Fig. No. 4: Compilation of Dissolution result of process optimization by RC method.

CONCLUSION

The Formulation of Ziprasidone Hydrochloride Capsules was successfully developed and optimized for immediate drug release profile & assay. The Capsules were prepared by dry compression method (Roller compaction) a Formula optimization carried out by 2^2 factorial design. The concentration Binding agent and Lubricating agent were important variables which shows effect on formulation.

Process optimization carried out by 2^{3-1} fractional factorial design. Screen used, pre-lubrication and lubrication time are important variables which show effect on formulation.
The evaluation results of optimized batch comply with USP criteria.

Accelerated stability studies shows that formulation is stable for 1 month.

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