Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
7(1), 2018, 07-13

ISSN 2321 – 0958

Original Research Article

QBD APPROACH IN FORMULATION AND EVALUATION OF ANTIMALERIAL AND ANTIBIOTICS AS COMBINATION THERAPIES

Vilas S Jadhav *and Dr. Deenanath Jhade

Sri Satya Sai University of Technology & Medical Sciences, Sehore, (M.P.)

Abstract: Since malaria is an illness that may rapidly progress to severe disease and even death, early diagnosis and prompt treatment of acute malaria episodes is an important strategy to reduce morbidity and mortality. The first and most important role of diagnosis is in patient management. Currently there is several medicines are available in the market and containing individual drugs. The major challenge in the malaria to provide or prescribe required dose to cure it in due course of time. The major part covered here to develop the combination therapy required to treat malaria to avoid over or low dose during the treatment. The main drug used in the treatment is Chloroquine and Azithromycin to cure in shortest period of time.

In present invention, the development of fix dose combination of Azithromycin and Chloroquine required treating malaria as most effective treatment. Based on overall literature search and studies, it was found that Azithromycin 250mg and Chloroquine 200mg are most suitable strength and combination to be used to trate the malaria. The objective of the present study was to formulate suspension of Azithromycin dihydrate (AZT) and Chloroquine (CQ) as fix dose combination useful to treat Malaria. Individually, Azithromycin and Chloroquine tablets are available in the market to treat malaria. However, there is no fix treatment dose are given during treatment. The present study is to develop safest and effective fix dose combination of Azithromycin and Chloroquine tablets.

Key words: Azithromycin, Chloroquine, Quality By Design, Malaria, Fix dose combination.

Introduction: Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, noninvasive method and ease of administration leading to high level of patient compliance. Pediatric and geriatric patients may suffer from ingestion problems as a result of underdeveloped

For Correspondence:
vilas.jadhav27@gmail.com.
Received on: February 2018
Accepted after revision: March 2018
DOI: https://doi.org/10.30876/johr.7.1.2018.7-13

muscular and nervous control [1].The development of Azithromycin 250mg and Chloroquine 200mg Tablets was initiated based on general pharmaceutical techniques and drug substance characteristics. The development objective was to prepare a prototype formulation comparable in performance with individual available products in the markets. The robustness of the formulation and process was established by preparing several experimental batches at the laboratory scale.

The quality-by-design (QbD) approach used in development of combination therapy for antimalarial-antibiotics using Azithromycin (Antibiotics) and Chloroquine (Antimalarial) drugs. The design space is defined as a manufacturing area of the product including Equipment, Material, and Operators and Manufacturing Conditions. The design space should be well defined prior to regulatory approval. Working with design space is not considered as a change, but working out of design space is considered as a change. Different variables are monitored for their effect of product quality when the manufacturing is done out of design space. All these variables are assessed and conclusions will be drawn which serves as a tool to QbD. Before conducting the development studies the QTPPs of the product must be determined and having the final product quality in mind and evaluation is performed to obtain the desired quality of product. The QTPP of product includes design space, specifications and manufacturing controls. In this paper, we used QbD approach for better understanding of relationship of critical formulation and process parameters to CQAs relating to quality product profile of Fix dose combination of Azithromycin and Chloroquine Tablets 250mg and 200mg. In present research paper, we are evaluating Effect of binder quantity, Binder addition time and Time of Granulation (Kneading time) on Granule properties and Dissolution profile using DOE (Design of Experiment)

Materials and method

Materials

Azithromycin was obtained from Ciron Pharma Pvt. Ltd., Mumbai;Chloroquine was obtained from IPCA Laboratory,Sodium Lauryl Sulphate, Povidone K 90, Crospovidone CLF, Crospovidone CLF are obtained from BASF, Microcrystalline cellulose obtained from FMC and Talc was obtained from Luzenac and film coating material was obtained from Colorcon.

Methods

Azithromycin is having poor flow properties hence wet granulation approach was adopted to develop the formulation. The prototype formulation developed considering all basic requirements of product characteristics and desired quality target product profile.

Table 1 Granulation Process Optimization Trials

Factors: Process Variables		**Levels**		
		-1	**0**	**+1**
A	Binder quantity (%)	5	10	15
B	Binder addition Time (min.)	2	4	6
C	Kneading Time (min)	1	3	5
Responses				
Y_1	Granules properties (BD/TD/PSD/Flow properties)			
Y_2	Disintegration Time (min)			
Y_3	Dissolution profile of Azithromycin			
Y_4	Dissolution profile of Chloroquine			

2^3 replicate full factorial designs are selected for process parameter optimization. Table 2 presents the study design. Small-scale laboratory trial batches were manufactured with different above mentioned process parameter, to study the effect on disintegration time and dissolution of the finished product.

Table 2 DOE Results For The Effect Granulation Parameter:

Parameters observation / Batch no	Binder Quantity (%)	Binder addition time (min)	Kneading time (min)	Disintegration time (R1)	Azithromycin Drug release	Chloroquine Drug release
13	15	6	5	36	78	88
9	15	6	1	35	91	92
10	15	2	5	24	91	98
3	15	6	1	32	98	100
1	5	2	1	29	96	103
12	15	6	1	21	98	99
17	10	2	1	32	100	101
6	5	2	1	29	96	102
16	15	2	5	24	93	99
11	15	6	5	35	85	95
4	15	2	5	58	86	97
15	15	6	1	24	98	99
2	5	4	3	32	99	102
7	15	6	5	31	102	105
14	5	6	5	31	100	103
8	15	2	5	55	87	98
5	5	2	1	36	98	99

Significant Factors Affecting On Disintegration Time

ANOVA for selected factorial model

Table3: Analysis Of Variance Table [Partial Sum Of Squares - Type III] (Adjusted)

Source	Sum of Squares	df	Mean Square	F value	p-value prob > F	Comments
Model	1492.75	5	298.55	45.79	< 0.0001	significant
A-Binder quantity (%)	240.25	1	240.25	36.85	< 0.0001	
B-Binder addition time	110.25	1	110.25	16.91	0.0017	
C-Kneading time	196.00	1	196.00	30.06	0.0002	
AB	484.00	1	484.00	74.23	< 0.0001	
AC	462.25	1	462.25	70.90	< 0.0001	
Residual	71.72	11	6.52	--	--	
Lack of Fit	49.72	3	16.57	6.03	0.0189	significant
Pure Error	22.00	8	2.75	--	--	
Cor Total	1564.47	16	--	--	--	

Based on the ANOVA results, stastically the selected model is significant with considered level of the process parameters for the tablet disintegration time response.

As shown in the half-normal plot (Figure 1), the significant factors affecting disintegration time are A (Binder quantity) and B (Kneading time) and combination of AB and AC.

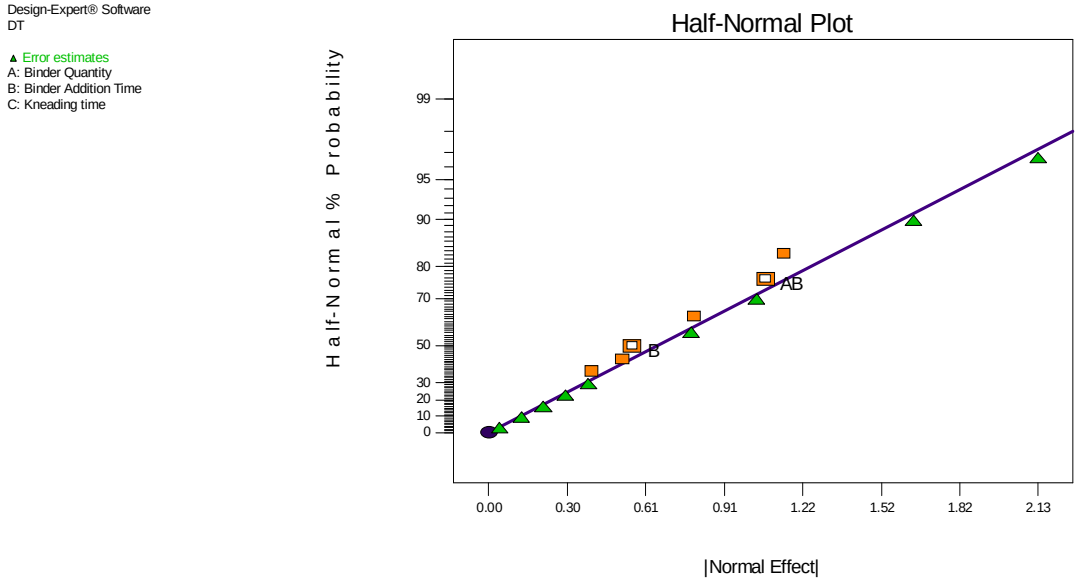

Figure 1: Half-normal plot of the process variable effects on Disintegration time of Azithromycin and Chloroquine Tablets

Figure 2 shows the effect of Binder quantity (%) and Binder addition time on tablet disintegration time. Disintegration time of tablet increases with increasing in Binder quantity.

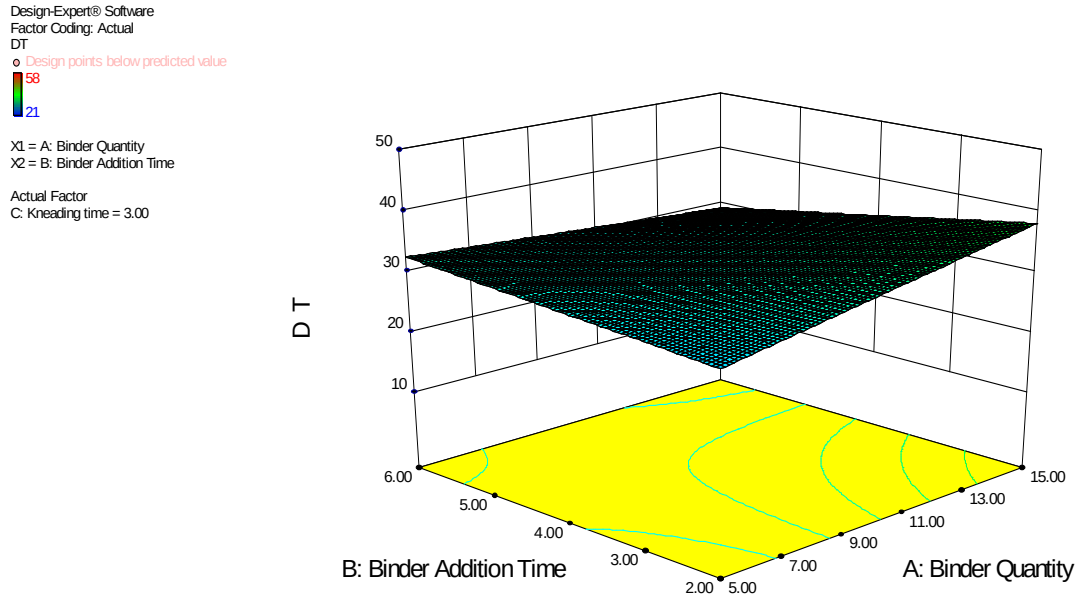

Figure 1: Effect of granulation process variables on disintegration time of Azithromycin and Chloroquine Tablets

Significant Factors for Dissolution At 30 Min: ANOVA for selected factorial model

Table 3 Analysis of variance table [Partial sum of squares - Type III] (Adjusted)

Source	Sum of Squares	df	Mean Square	F Value	p- value prob > F	Comments
Model	1618.19	3	539.40	19.76	< 0.0001	significant
A- Binder quantity	60.06	1	60.06	2.20	0.1618	
C- Kneading time	612.56	1	612.56	22.44	0.0004	
AC	945.56	1	945.56	34.64	< 0.0001	
Residual	354.87	13	27.30	--	--	
Lack of Fit	270.37	5	54.07	5.12	0.0211	significant
Pure Error	84.50	8	10.56	--	--	
Cor Total	1973.06	16	--	--	--	

Based on the ANOVA results, stastically the selected model is significant with considered level of the process parameters for the tablet dissolution at 30 min response.

As shown in the half-normal plot (Figure 3), the significant factors affecting dissolution at 15 min were A (API addition time) and C (Kneading time) and combine effect of both.

Figure 3 shows the effect of Binder quantity (%) and Binder addition time on Azithromycin Drug release and Figure 4 shows effect on drug release of Chloroquine.

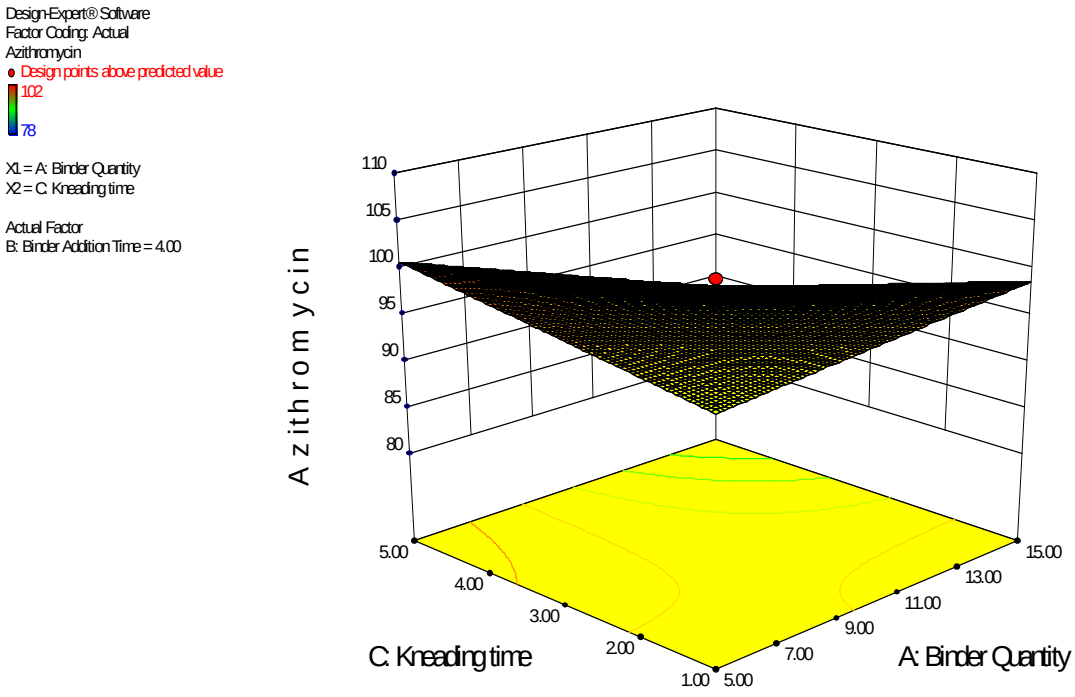

Figure 3: Effect of granulation process variables on Azithromycin Drug release.

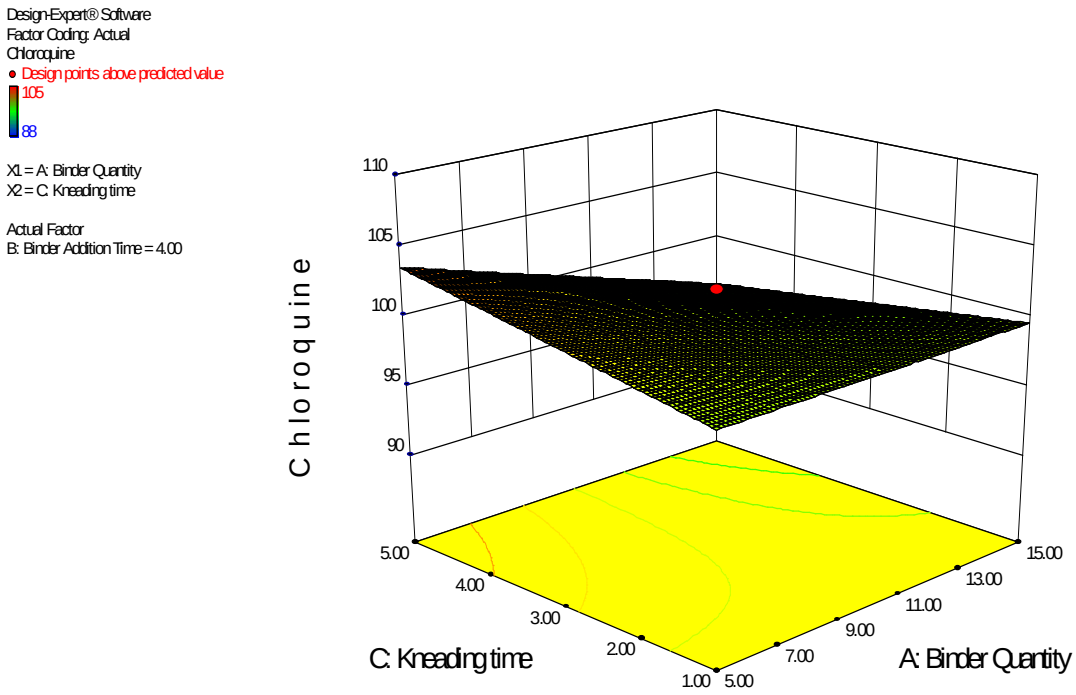

Figure 4: Effect of granulation process variables on Chloroquine Drug release.

Results and Discussion: Significant factors for tablet dissolution at 45 min.: For responses dissolution at 45 minutes performed and no significant difference observed. Complete release observed at these time points.

Binder addition time had a significant impact on disintegration time and tablet dissolution at 45 min. Dissolution decreased with increasing binder addition time.

Binder addition time and Kneading time showed impact on tablet disintegration time dissolution at 45 min .Kneading time has significant impact on tablet dissolution at 45 min.

Conclusion: The Experiments performed by Quality by Design are sufficient to identify the critical process parameters and design space to have good quality product.

Acknowledgement: Authors are thankful to Ciron Pharma Pvt. Ltd., Mumbai and IPCA Laboratory, India for providing gift samples of azithromycin and Chloroquine. Also would like to thanks for all excipients suppliers for their great support.

References

1. Vilas S Jadhav, Pankaj Chandratreya. Formulation and Evaluation of Floating tablet of Gliclazide usingHPMC and Xanthan Gum.; International Journal of PharmTech Research,;2014-2015, 7(1): 132-138.
2. Kuchekar, B. S., Atul, B.C., Mahajan, H.S.: Mouth dissolving tablets: A novel drug delivery system. Pharma Times. 2003,35,7-9.
3. Ashok Thulluru, M. Mohan Varma, C. M. Setty, A. Anusha, P. Chamundeeswari, Sk. Sanufar Formulation, In vitro and In vivo Evaluation of Pioglitazone Hydrochloride - Effervescent Gastro Retentive Floating Hydrophilic Matrix Tablets. International Journal of PharmTech Research,;2016 388-398,
4. Hussar, D.A.: New drugs of 2003. J. Am. Pharm. Assoc. 2004,44, 168–206.

5. Porst, H., Padma-Nathan, H., Giuliano, F., Anglin, G., Varanese, L.,Rosen, R.: Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology.2003; 62, 121–126.
6. Padma-Nathan, H.: Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction, Am. J. Cardiol. 2003;92, 19M–25M.
7. Higuchi, T., Connors, K.A.: Phase-solubility techniques Adv.Anal.Chem.Instr., 1965;4,117-122.
8. LachmmanL,LibermanHA,KonigJl. The theory & practice of industrial pharmacy,3rd Edn,Vargheese publishing house, Bombay,1991:297-300.
9. Indian Pharmacopoeia Government of India 2010.
10. Jha, S., Vijayalakshmi, P., Karki, R., Goli, D.: Formulation and evaluation of melt-in-mouth tablets of haloperidol. *Asian J. Pharm.2008;* 255-260.
11. Ravikumar, S.R., Patil, M.B., Patil, M.S.: Design and Characterization of aceclofenac mouth dissolving tablets by effervescent formulation approach. Int. J of Pharm Sci., 2010; 2, 220-236.
12. Mangal, M., Thakral, S., Goswami, M., Thakur, N. Comparison Study between Various Reported Disintegrating Methods for Fast Dissolving Tablets. African J of Basic and Applied Sci., 2012; 4(4), 106-109.
13. Kraemer, J., Gajendran, J. Guillot, A., Schichtel, J., Tuereli, A.: Dissolution testing of orally disintegrating tablets. Journal of Pharm. Pharmacol.2012; 64(7), 911-918.
14. Kulkarni, A.P., Khedkar, A.B. Lahotib, S.R., Dehghan, M.H.D.: Development of Oral Disintegrating Tablet of Rizatriptan Benzoate with Inhibited Bitter Taste. American- Eurasian Journal of Scientific Res., 2012; 7(2): 47-57.
15. Patel B.P, Patel J.K, Rajput G.C, Thakor, R.S.: Formulation and evaluation of mouth dissolving tablets of cinnarizine. *Indian J. Pharm. Sci., 2010;* 72(4) 522-25.
16. Kalaivanan, M., and K. Vengatesan. "Recommendation system based on statistical analysis of ranking from user." International Conference on Information Communication and Embedded Systems (ICICES), , pp. 479-484. IEEE, 2013.
17. Higuchi, T., Connors, K.A.: Phase solubility techniques, in: C.N. Reilly (Ed.), Advances in Analytical and Chemistry Instrumentation, vol. 4, Wiley Interscience, New York,1965; pp. 117–212.
18. Loftsson, T., Masson, M., Brewster, M.E.: Self association of cyclodextrin and cyclodextrin complexes, J. Pharm. Sci.2004; 93, 1091–1099.