Design and Development of Medicated Chocolate Containing Anti-depressant drug

ZALAK SHARMA[1], DR. NIKITA CHAUHAN[2], BHAKTI SHAH[3]

Assistant professor, department of pharmaceutics, shree swaminarayan sanskar pharmacy college , zundal, gandhinagar -382421
Associate professor, department of pharmaceutics, khyati college of pharmacy, palodia gujarat-3820058
Assistant professor, department of pharmaceutics, shree swaminarayan sanskar pharmacy college , zundal, gandhinagar -382421

ABSTRACT:- ***Objective****: Design and development of medicated chocolate containing anti-depressant drug – Amitriptyline HCl. The formulation is optimized by Factorial design method. The main aim is To increase the patient compliance and reduce the rejection towards the other pharmaceutical products.* ***Experimental Work:*** *The medicated chocolate of Amitriptyline HCl is formulated using cocoa powder, cocoa butter, Mannitol and other suitable excipients. The bitter taste of the drug is masked by using beta cyclodextrin. Various trial batches are formulated to obtain the maximum drug release. 23 factorial design was employed for the optimization of the formulation. Pre formulation and post-formulation studies were done for the evaluation of the formulation.* ***Result:*** *The medicated chocolate containing Amitriptyline HCl (10mg) showed 97.2% drug release after 1 hour. The formulation has passed all the evaluation parameter. For stability improvement, Mannitol was added. The taste was also enhanced due to addition of mannitol.* ***Conclusion****: The studies indicates that the formulation is acceptable for the patients who are formed to get better taste, texture and also to decrease the level of rejection towards medications which has bitter taste.*

Key Words: *Medicated chocolate, Amitriptyline HCl, Beta cyclodextrin, 2^3 full factorial design.*

I. INTRODUCTION

Every prescription now a days contains several divisions of pharmaceuticals that must be delivered at regular intervals, most commonly by oral route. This type of repetitive oral administration of multiple treatments makes the patient uncomfortable due to swallowing difficulties. Patient compliance can be improved by delivering active ingredient in a visually attractive manner, which reduces rejection and psychological inhibition towards dosage forms.(1) Chocolate is a highly sophisticated and much adaptable food that can be combined to create completely different taste and consistency sensation. Chocolate is also an anhydrous medium and is therefore resistant to microbial growth and to hydrolysis of water-sensitive active agents.(2) Chocolate abundantly contains compounds such as saturated fat, polyphenols, sterols, di and tri terpene, aliphatic alcohols and methyl xanthines.(3)

II. MATERIALS AND METHOD

Table No 1 List of Materials

Materials	Quantity	Use
Amitriptyline HCl	10mg	API
Cocoa powder	490mg	Key Ingredient
Cocoa butter	700mg	Key Ingredient
Lecithin	10mg	Stabilizer
Beta cyclodextrin	10mg	Taste masking agent
Pharmaceutical Grade Sugar	850mg	Sweetening agent
Methyl parabeen	0.01ml	Preservative
Mannitol	1750mg	Bulking agent

METHOD OF PREPARATION:

Preparation of Chocolate Base

Double boiler method was used for the preparation of chocolate base. All the ingredients for chocolate base were taken and sieved. In this mixture of ingredients melted cocoa butter was added. With the help of glass rod the mixture was stirred for getting a pourable consistency. Then add methyl paraben as a preservative. Careful attention was paid to the chocolate manufacturing process to ensure that the temperature was not too high.

Formation of Inclusion Complex by Kneading Method

The kneading method is also known as paste method, is a moderately simple method in which the beta cyclodextrin is weighed and mixed with a small amount of purified water in a mortar to obtain a paste. Then the same amount of drug is weighed and is mixed with the paste with thorough mixing to obtain 1:1 molar ratio of drug and beta cyclodextrin. The paste was dried to obtain solid mixture. This mixture was passed through sieve no. 60.

Formulation of Medicated Chocolate

Oven was preheated. The chocolate base was melted to obtain free pourable liquid. The inclusion complex of drug and beta cyclodextrin was added with continuous stirring. Above mixture was filled in to a mould and refrigerated till it become solid.

III EVALUATION OF FORMULATION

Pre-formulation Studies

Determination of ʎ-max of Amitriptyline HCl

50mg drug was taken in 50mL volumetric flask and dissolved in 50mL 7.4pH phosphate buffer. From this solution, 5mL is taken in 50mL volumetric flask and the volume was made up with7.4pH phosphate buffer solution. From this stock solution pipet out 1mL and place into 10mL volumetric flask. Volume was made up to mark with buffer solution to get solution containing10 µg/mL, which was further diluted with same and scanned between wavelength of 200-400nm

Calibration Curve of Amitriptyline in 7.4 pH Phosphate Buffer and in saliva solution (6.8pH)

50mg drug was taken in 50mL volumetric flask and dissolved in 50mL 7.4pH phosphate buffer. From this solution, 5mL is taken in 50mL volumetric flask and the volume was made up with 7.4pH phosphate buffer solution. From this stock solution 0.5, 1, 1.5, 2, 2.5 mL solutions are taken in 10mL volumetric flask and the volume was made up using 7.4pH phosphate buffer solution to obtain 5,10,15,20,25 µg/mL solutions respectively. The absorbance of these solutions was determined by UV Spectrophotometer at 239nm and calibration curve was plotted.

Solubility profile of drug

Solubility is one of the most important parameter to achieve desired concentration of Drug was dissolved in water, ethanol, chloroform, acetone and diethyl ether at room temperature.

Melting Point Determination

Melting point of the drug is determined by using melting point apparatus. This was compared to the official melting point value of the drug.

Drug-Excipients Interaction Study

To study the compatibility of various formulation excipients with amitriptyline, solid mixtures were prepared by mixing the drug with each formulation excipients separately in the ration of 1:1. Solid admixtures were characterized using Fourier transform infrared spectroscopy(FTIR).

DSC Analysis of Inclusion Complex

DSC scan of powdered samples of drug, beta cyclodextrin and kneaded inclusion complex were recorded using DSC instrument

Evaluation of Medicated Chocolate

General Appearance: The general appearance of medicated chocolate in terms of colour, shape, texture and consistency was evaluated by visual inspection. Texture was observed by rubbing the formulation between two fingers.

Hardness of Chocolate Chocolate crushing strength was measured by Pfizer hardness tester. The hardness of a medicated chocolate should not be more than 5kg/cm2.

Blooming Testes

Fat Bloom When a layer of fat crystals develops on the top of the chocolate and waits to be melted. The dulling of the chocolate and the appearance of a fluffy white covering are both unpleasant outcomes.

Sugar Bloom Sugar bloom is characterised by a white, dusty, grainy coating that appears on the surface of chocolate

Moisture Content Determination A desiccator was used to determine moisture content. The chocolate is weighed precisely and was kept in a desiccator containing anhydrous silica gel. After 24 hours the chocolate was taken out from the desiccator and weighed again.

Drug Content Determination: Drug content of medicated chocolate is determined by UV spectrophotometer.

Weight Variation Test: To study weight variation individual weights (wI) of 5 chocolates from each formulation were noted using electronic balance. Their average weight (Wa) was calculated.

In Vitro Drug Dissolution Study: The in vitro drug release studies were carried out on a eight stationed USP type II dissolution apparatus at 37°C±0.5°C and 50 rpm for a period of 1 hour using 7.4pH phosphate buffer solution as a dissolution media.

Factorial Design Experiment: A 2^3full factorial design was employed to evaluate the selected variables. The concentration of cocoa butter(X1), mannitol(X2) and blending time(X3) were selected as the independent variables whereas hardness(Y1) and %drug release(Y2) selected as dependent variables. The data were analysed by using design expert software.

Accelerated Stability Study Stability studies was done according to ICH guidelines[Q1A(R2)]. The formulation was packed in aluminium foil and kept in wide mouth air tight container, kept in a room temperature (25±5°C, 75%±5 RH) and refrigerated temperature (0-8°C) for 1 month.

IV RESULT AND DISCUSSION

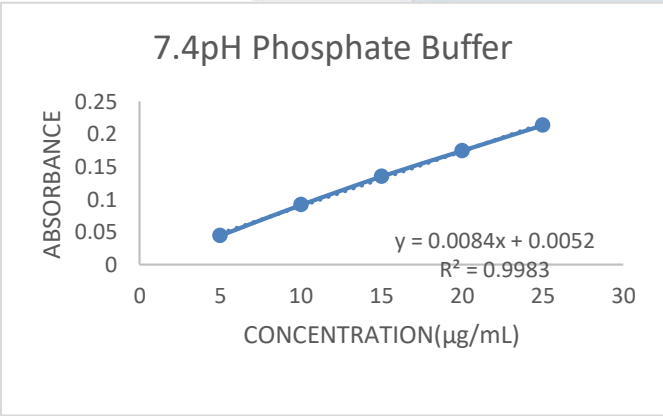
Results of Pre-Formulation Study

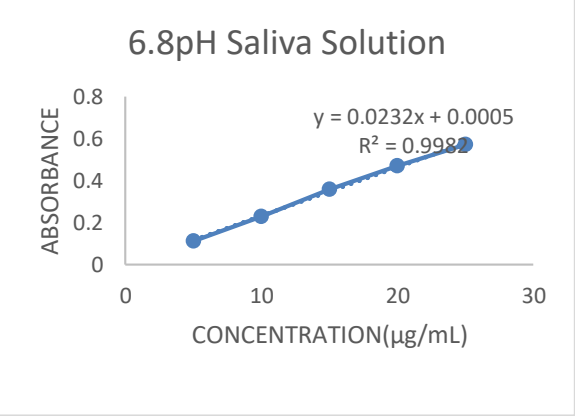
Absorbance Maxima

The λ_{max} of the drug is 239nm

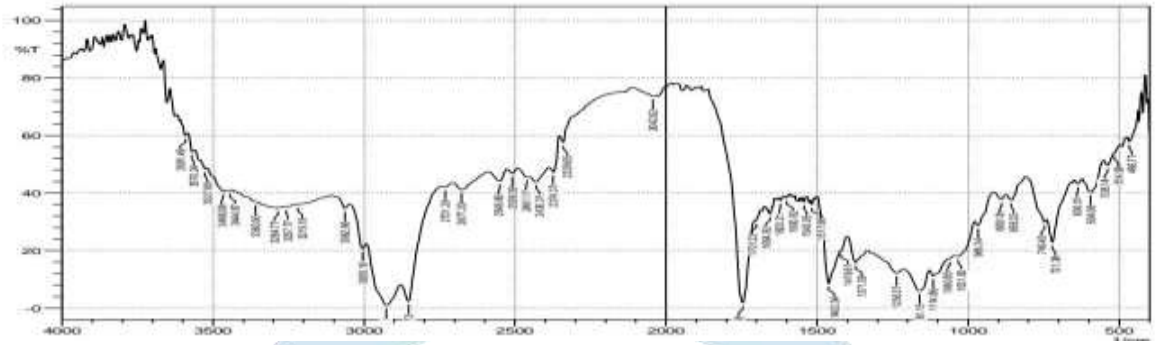
Melting Point : The melting point of the drug is 194 - 198°C.

Figure :1 Calibration Curve of Amitriptyline **Figure2 Calibration Curve of Amitriptyline**





Fgure: 3 FTIR of Physical Mixture (Drug + Cocoa Powder+ Cocoa Butter + β-CD)



Fgure: 4 DSC of Drug + β – CD (1:1)

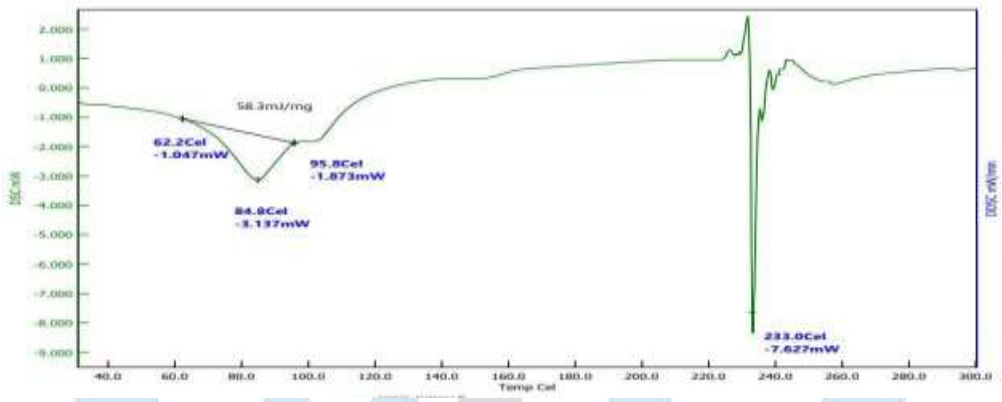


Table No 2 General appearance of batch

Formulation	Colour	Shape	Odour	Appearance	Stickiness	Fat bloom or Sugar bloom
F_1	Dark brown	Square	Chocolaty	Good	No	No
F_2	Dark brown	Square	Chocolaty	Good	No	No
F_3	Dark brown	Square	Chocolaty	Very good	No	No
F_4	Dark brown	Square	Chocolaty	Good	No	no
F_5	Brown	Square	Chocolaty	Very Good	No	No
F_6	Brown	Square	Chocolaty	Very good	No	No
F_7	Dark brown	Square	Chocolaty	Good	No	No
F_8	Dark brown	Square	Chocolaty	good	No	No

Table No 3 Evaluation of factorial batch

Formulation	Hardness (kg/cm^2) n=3 ±SD	Thickness (mm) n= 3 ±SD	%Moisture Content n= 5±SD	Weight Variation n= 3 ±SD	%Drug Content
F_1	3.62±0.01	7.39±0.01	1.08 ± 0.01	2.66±0.001	90.5 ± 0.04
F_2	3.14±0.02	8.14±0.03	1.40 ± 0.03	3.24±0.004	93.2 ±0.02
F_3	4.13±0.02	7.98±0.02	0.89 ± 0.02	3.44±0.002	94.6 ± 0.01
F_4	3.88±0.01	9.06±0.01	0.54 ± 0.03	3.24±0.003	93.8 ± 0.02
F_5	4.12±0.03	8.88±0.01	1.35±0.002	2.87±0.002	92.6± 0.02

F_6	3.72±0.02	8.79±0.03	1.13±0.004	3.12±0.002	97.2± 0.01
F_7	3.97±0.01	8.28±0.01	0.95±0.002	2.59±0.004	92.9± 0.02
F_8	2.98±0.02	8.49±0.02	1.75±0.002	3.08±0.001	95.5± 0.03

Figure 5 Medicated Chocolate

Figure6 In vitro Release Study

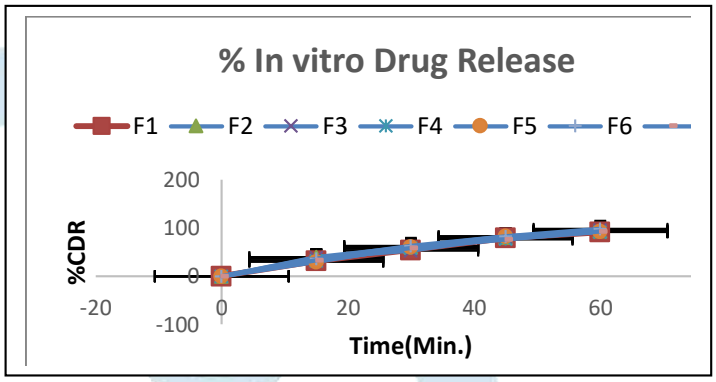


Figure 7 3D Contour Plot Graph for Hardness

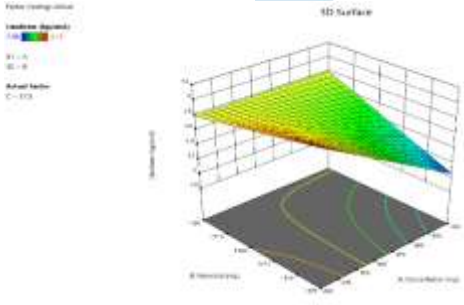


Figure 8 3D Contour Plot Graph for %drug Release

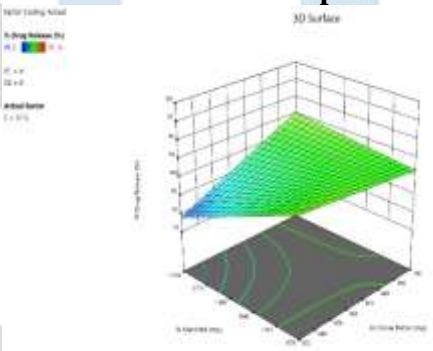


Table No 4 ANOVA Response

Source	Sum of Square	df	Mean Square	F-Value	p-Value	
Model	1.31	6	0.2175	4350.50	0.0116	Significant
A= Cocoa Butter	0.5618	1	0.5618	11236.00	0.0060	
B=Mannitol	0.0841	1	0.0841	1681.00	0.0155	
C=Blending Time	0.0162	1	0.0162	324.00	0.0353	
AB	0.5724	1	0.5724	11449.00	0.0059	
AC	0.0162	1	0.0162	324.00	0.0353	
BC	0.0544	1	0.0544	1089.00	0.0193	
Residual	0.0020	1	0.0020			
Cor Total	1.31	7				

Accelerated Stability Study

Stability studies was done according to ICH guidelines [Q1A(R2)]

Table No 5 Stability study data

Parameter	initial	After 1 Month (At Room Temperature 25±5°C,60%±5 RH)	After 1 Month (At Refrigerated Temperature28°C)
Colour	Dark Brown	Dark Brown	Dark Brown
Appearance	Very Good	Good	Very Good
Stickiness	No	No	No
Fat bloom or Sugar bloom	No	No	No
Drug Content (%)	97.2± 0.02	96.7± 0.02	97.0± 0.01
%Drug Release	97.1± 0.01	96.8± 0.01	96.9± 0.02

V CONCLUSION

The aim of the work was to develop a dosage form which helps to improve and enhance the patient compliance. Amitriptyline – a bitter tasted drug is converted into chocolate dosage form to make it more acceptable by the patients. All the parameters are evaluated and the results were satisfied. F6 formulation has the highest drug release of 97.2% after 60 minutes. The 2^3 full factorial design was applied, the results of the optimization were also significant.

VI REFERENCES

1. Lakshmi P., Sudhakar B., Revathi K., Ashok K., Uday K., Formulation and evaluation of chocolates consisting of guaifenesin, European Journal of Pharmaceutical and Medical Research, 2018.
2. **.** Mayank S., Dinesh Kumar J., Chocolate formulation as drug delivery for paediatrics,2012. Judy Davis, San Clemente, CA and Patent no. 0004604: dark chocolate delivery systemfor a combination of dietary supplements and pharmaceuticals, 2013. Mayank S., Dinesh Kumar J., Chocolate formulation as drug delivery for paediatrics, 2012.
3. Judy Davis, San Clemente, CA and Patent no. 0004604: dark chocolate delivery system for a combination of dietary supplements and pharmaceuticals, 2013
4. https://www.slideshare.net/rahulbs89/depression.3557197
5. https://www.researchgate.net/publication/284651508
6. https://www.tandfonline.com/doi/epdf
7. https://images.app.goo.gl/VUb09K06hFKjTzm29
8. Mayank S., Kumar JD, chocolate formulation as drug delivery system, Indonesian Journal of Pharmacy, 2012.
9. Sonak S., Trivedi S., Wadher K., Umekar M., International Journal of Modern Pharmaceutical Research, 2019: 3(6).
10. https://www.suite101.com/article.cfm the human tongue anatomy cited on 15 September, 2011.
11. Patel ND, Shukla SK, Tomar P., Jain H., Pradhan P, Upadhyay U., Chocolate drug delivery system: a review, Indo-American journal of Pharmaceutical Sciences, 2015:2(6):1077-1081.
12. Ackar D., Valek Lendic K, Valek M., Nedic J., Cocoa polyphenols; can we consider cocoa and chocolate as potential functional food, Journal of chemistry, 2013: 1-7.
13. Pawar PG, Darekar AB, Saudagar RB, Medicated chocolate and loli[pops: a novel drug delivery system for paediatric patient, Pharma Science Moniter, 2018: 9(1).
14. Chaudhary SA, Deware RR, Dewang PS, Patil VB, Patil AM, Pawar SP, Review: chocolate formulation as drug delivery system, Indian Journal of Drugs, 2018:6(2):136-141.