FORMULATION DEVELOPMENT AND OPTIMIZATION OF CHOCOLATE DOSAGE FORM CONTAINING DOMPERIDONE

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Abstract

Introduction: Poor adhesion to medication is a common problem encountered in case of pediatric patients. Besides various reasons, one way to overcome is modification of the form which it appears to pediatrics. Drug incorporation in chocolate may mask the inhibitory feeling of medication in children. The aim of the work is to optimize a chocolate dosage form containing domperidone using response surface methodology.

Methods: Drug is complexed with beta cyclodextrin to increase solubility. Chocolate base is prepared using cocoa powder, cocoa butter, milk powder, mannitol and soya lecithin as formulation additives. Prepared medicated chocolates were evaluated for organoleptic properties, drug content and drug release studies. Optimization of the formulation was done using 3^2 full factorial design. Concentration of cocoa butter (X_1) and concentration of sweetening agent (X_2) were taken as independent variable. The independent variable selected were hardness, melting point and percentage drug release at 15minutes. Polynomial equations and response surface plots were generated for all the dependent variables.

Results: Concentration of the coca butter had a negative effect on drug release indicating it as a primary factor to be considered. Concentration of sweetener has positive effect on all the responses. Hardness of the medicated chocolates varies in the range of 1.5 – 3.1 kg/cm^2. Drug from all the chocolate dosage forms was found to release within 45min. Stability study indicates that the formulation is intact with negligible variation in the evaluation parameters.

Conclusion: It was observed from the results that medicated chocolates have appreciable organoleptic properties with acceptable drug release.

Keywords: Contour plots, medicated chocolate, polynomial equations, response surface methodology.

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DOI: 10.48047/ecb/2023.12.si5a.0303

INTRODUCTION

Among various routes of administration oral route is most convenient and preferred route for many drugs and for all age groups. Manipulation of adult oral doses like crushing or cutting or diluting is commonly practiced among pediatrics. This results in bioavailability and accuracy issues along with poor acceptance.[1] Dose size, taste masking, accuracy of dose, unchanged therapeutic efficacy with global acceptance are hurdles to be crossed during development of a pediatric formulation. [2] As pediatrics include wide range of age group a single form cannot fulfill the requirements of pediatric dosage form along with therapeutic efficacy. A proper pediatric formulation with desirable taste and pharmacological features need to be developed for improved pediatric patient compliance. Rejection towards medication can be overcome to some extent by converting the form it appears to pediatrics. The most attractive and admired form by children is chocolate. So an attempt is being made to formulate chocolate as a pharmaceutical dosage form. [3, 4]

Chocolate, a sound of sweet has been ruling the world of food since ancient period. It has been transformed as a delicious food to preferred form of prescription. It has smooth texture and good mouth feel taste which can be utilized to mask the bitterness of drugs. Anhydrous medium of chocolate helps to incorporate drug without degradation. The flavonoids, principle ingredient of chocolate also helps in protective action of drug. Because of its versatility and world wide acceptance an attempt has been made to incorporate drug in it. [5]

Domperidone is used for short term treatment of nausea and vomiting. It is an antiemetic, prokinetic agent and also used in the treatment of migrane along with paracetamol. [6] Domperidone is commonly used antiemetic in pediatrics. So, domperidone is selected to be developed as chocolate formulation. Domperidone is a poorly water soluble drug and complexation with beta cyclodextrins is considered to improve its solubility. [7,8]

METHODOLOGY

Materials:

Domperidone is purchased from Natco, Hydera-bad. Coca powder, cocoa butter, skim milk powder, soya lecithin were purchased from local market. Mannitol is purchased from RFCL ltd. All other ingredients and reagents used in the study are of analytical grade.

Fourier transform infrared spectroscopy (FTIR):

Interaction and compatibility of drug with excepients was known by FT IR studies. The spectra of the samples (pure drug, drug with β-CD and drug with other excepients) were recorded at a range of 4000 – 400 cm^{-1} with an FT IR spectrophotometer using KBr disc method.

Preparation of inclusion complexes:

Domperidone was complexed with β-cyclodextrin to increase the solubility of drug by physical mixture and kneading method. Drug and β-CD in 1:0.5, 1:1, 1:1.5, 1:2 molar ratios were mixed in both the methods. In physical mixture method drug and β-CD of various ratios were mixed gently in mortar and pestle for 15minutes. In kneading method drug with β-CD in same ratios were triturated in mortar with small volume of water. The thick slurry was kneaded for 45min and dried at 50˚C. These mixtures were passed through sieve no 120 and then stored in a descicator for further use.

Solubility studies:

Solubility study was carried out as per Higuchi and Connors method. Excess amount of drug was added to the medium in the study. The solubility of domperidone, physical mixture and kneading method was determined in distilled water and 0.1N HCl. Drug and the carrier as per specified ratio was weighed and added to 10ml of media and the mixture was stirred for 24h at 37ºC. Then the mixtures were allowed to attain equilibrium and filtered. The concentration of drug in filtrate was determined by UV spectrophotometer at 285nm. Solubility data was given in Table 1.

Table 1: solubility study of complexes

Batches	Ratio	Solubility in media (mg/ml)	
		Distilled water	0.1N HCl
Pure drug	-	0.0091±0.47	0.995±0.21
DP1	1:0.5	0.0176±0.58	1.67±0.35
DP2	1:1	0.0323±0.92	3.28±0.52
DP3	1:1.5	0.0516±0.38	5.36±0.81
DP4	1:2	0.0698±0.75	6.99±0.53
DK1	1:0.5	0.0425±0.37	4.57±0.61
DK2	1:1	0.090±0.74	9.15±0.69
DK3	1:1.5	0.124±0.26	13.92±0.71
DK4	1:2	0.178±0.41	18.38±0.83

Preparation of the medicated chocolate:

Ratio of the drug complex to be incorporated in the medicated chocolate preparation was selected after solubility testing of the complexes. Pediatric equivalent dose of selected complex ratio along with the excepients were weighed accurately and sieved. Cocoa butter was melted on a water bath and mixture of cocoa powder, milk powder along with mannitol is added to it. High attention was paid to the process to ensure that the temperature of the mixture was not too high. The mixture was stirred about 30 min with glass rod to obtain smooth consistency. To this domperidone and β-CD complex, soya lecithin and sorbitan tri stearate were added with uniform mixing. The above mixture was then filled into polycarbonate mould and refrigerated for 1h till it solidified. Formulation of the medicated chocolates was given in Table 2.

Table 2: Composition of medicated chocolate

S. No	Ingredient	Quantity taken
1	Domperidone – β CD complex	0.020g
2	Cocoa powder	0.02g
3	Cocoa butter	0.12g
4	Milk powder	0.02g
5	Soya lecithin	0.002g
6	Mannitol	0.14g
7	Sorbitan tri stearate	0.002g
8	Methyl paraben	0.002ml

Experimental design:

A 3^2 full factorial design was employed to optimize the medicated chocolate formulation. A total of 9 experiments were carried out for two factors at three levels each. The experimental runs with observed response for 9 formulations are shown in Table 3. Polynomial equations, statistical parameters and response surface graphs for the responses were obtained by Design Expert software trial version.

Table 3: Process variable and responses in 3^2 full factorial design

Batch	X1	X2	Hardness	Melting point	% drug released at 15min
F1	-1	-1	1.5	28	46.1
F2	-1	0	1.8	29	49.2
F3	-1	+1	2	31.5	54.3
F4	0	-1	1.9	29.5	40.6
F5	0	0	2.2	31	43.1
F6	0	+1	2.5	32	48.3
F7	+1	-1	2.8	30	32.1
F8	+1	0	3.1	33	34.4
F9	+1	+1	3.1	35	36.3

Evaluation parameters:

Solubility evaluation of inclusion complex

Solubility studies of drug and β-CD complexes prepared by both the methods were indicated that there is increase in solubility of pure drug in the presence of beta cyclodextrins in distilled water and 0.1N HCl. When compared to physical mixture, complexes prepared by kneading method have shown good influence on solubility of drug. Solubility data of the study was given in Table 1.

General characterization of medicated chocolates

Colour, shape and texture in terms of stickiness and grittiness of the medicated chocolates were evaluated by visual inspection. Texture was observed by rubbing the formulation between two fingers. Smell or fragrance and taste of medicated chocolates were observed by the human volunteer panel which is considered for identification of complex taste. [9]

Hardness

Formulations were tested for hardness by using pfizer hardness tester. From each batch three medicated chocolates were measured for the hardness and average was taken.

Determination of drug content

Medicated chocolate was taken in a beaker and dissolved in 10ml of water and sonicated. Then the mixture was centrifuged for 10 min at 2500 rpm. Clear supernant liquid containing drug was filtered to remove traces of chocolate if any present in it. Then the liquid was analyzed by UV spectrophotometer against water as a blank at 285nm. [10]

In vitro dissolution test

Drug release from the medicated chocolate was assessed using USP type II dissolution apparatus in 900 ml of 0.1N HCl at 50 rpm maintained at 37˚C ± 0.5˚C for 60 min. An aliquot of 5ml was withdrawn at predetermined intervals and replaced with same volume of preheated fresh dissolution medium. The samples were filtered through whatmann filter paper and analyzed by UV spectrophotometer at 285 nm. The drug release studies were carried out in triplicate. The amount of drug released was calculated and % release Vs time graphs were plotted. [11]

Stability studies:

Stability studies were carried out for optimized formulation according to short term stability study. Optimized formulation was packed in aluminium foil and stored at different conditions like air tight container, specified temperature (25±5˚C) and refrigerated conditions (0-8˚C) for 3 months. Stability of the formulation was assessed by observing physical parameters such as appearance, smell, color, melting point, hardness and also percentage drug release. [10]

STATISTICAL ANALYSIS

Optimization of formulations is done using Design Expert software trial version. Contour plots and response surface plots are drawn using the software. Optimized concentrations are considered from the results after application of factorial design.

RESULTS AND DISCUSSIONS

FTIR studies:

FT IR studies of drug and excepients did not show any significant shifting of bonds compared to the pure drug indicating good compatibility between the ingredients. It indicates that the change in molecular level of drug is due to complexation observed in spectra. IR spectra of the pure drug, drug with beta cyclodextrins and other formulation ingredients were shown in Figure 1-3.

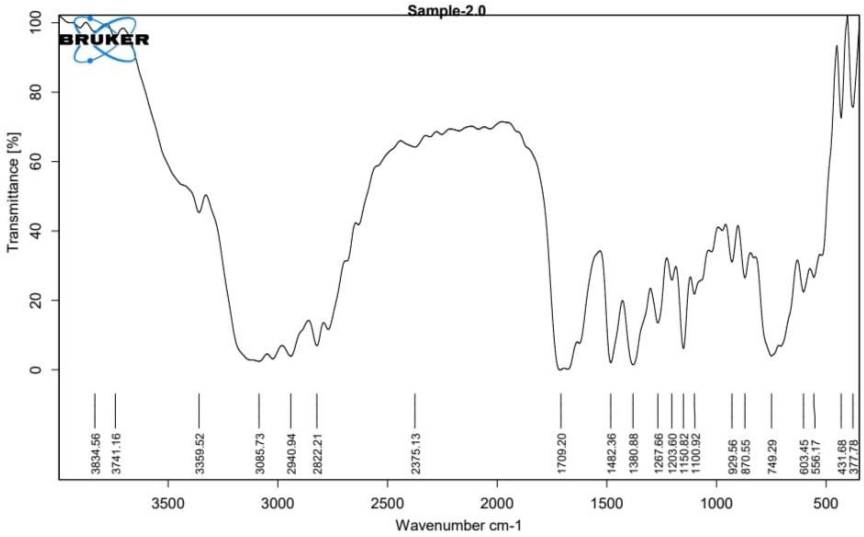

Figure 1: FTIR of pure drug domperidone

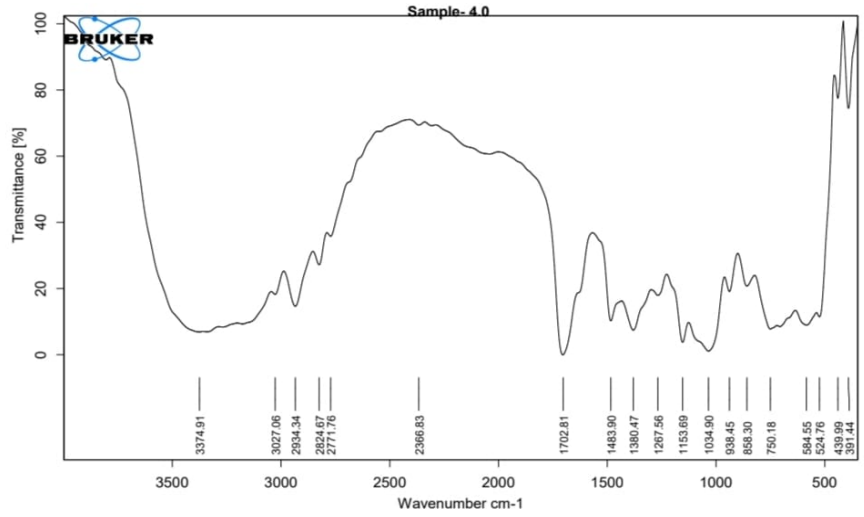

Figure 2: FTIR of drug and beta cyclodextrins

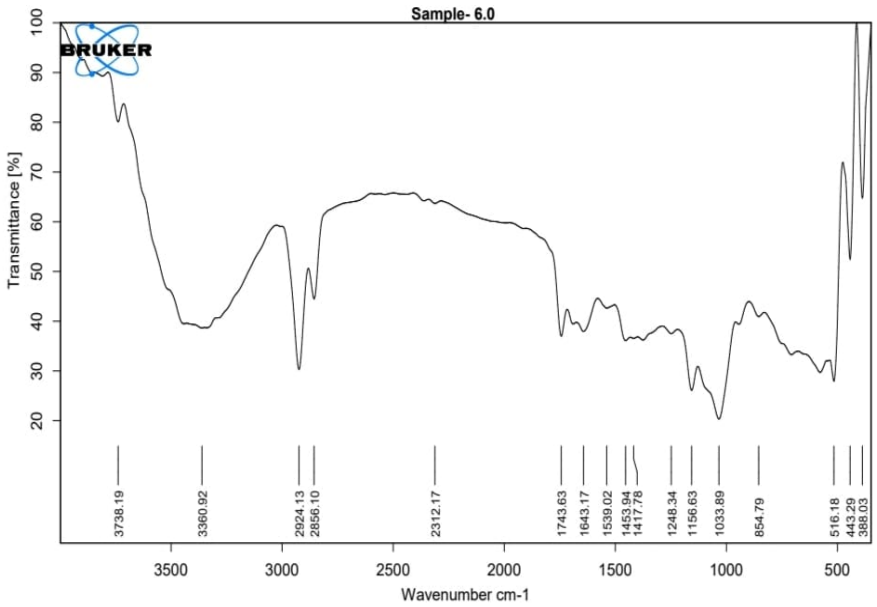

Figure 3: FTIR of drug and formulation excepients

Physical characterization of medicated chocolates:

All the chocolates are brown in color with chocolaty fragrance and glossy appearance. All the formulations are non sticky having smooth texture without any gritty particles. All the chocolates are in permissible limits of weight variation (i.e., 5%). The drug content of all the formulations was found to be in the range of 93.4% - 99.2% with uniform distribution of drug.

Drug content of the formulationsis reported in Table 4.

Table 4: Drug content of ondansetron chocolates

Batch	Drug content
F1	96.1±0.03
F2	93.4±0.07
F3	94.9±0.02
F4	97.5±0.01
F5	95.3±0.05
F6	99.2±0.06
F7	96.8±0.01
F8	97.1±0.04
F9	95.4±0.02

Optimization by experimental design:

Evaluation parameters obtained for the formulations were fitted into multiple regression analysis. The factors selected are concentration of coca butter and concentration of sweetening agent. The responses selected are hardness, melting point and % drug released at 15min. mathematical relationships of the dependent and independent variables are generated as equations and were given below.

Hardness = +2.32+0.6167A+0.2333B
Melting point = +31.0+1.58A+1.83B
% Drug released at 15min = +42.71-7.80A+3.35B

The correlation coefficients of the responses indicate good agreement between dependent and independent variables. Magnitude of the coefficient and the mathematical sign it carries can be utilized to draw the conclusions. Positive sign before the factor indicate that the increase in the factor increase the response where as the negative indicates reciprocal relationship between the dependent and independent variables. From the above equations it is clear that concentration of the cocoa butter and mannitol has a positive effect on the hardness and melting point. As the concentration of the both variables increases responses also increased. Concentration of manitol has positive effect on percentage drug release at 15min Whereas concentration of cocoa butter has negative effect on drug release indicating that the increase in concentration of butter decreases the drug release. The quadratic models generated by the regression analysis are used to construct 3D response surface plots. ANOVA table of the dependent variables was given in Table 5. Multiple regression analysis of responses indicate that the both factors had significant effect ($p<0.05$). Response surface plots and Contour plots obtained from the experimental design were shown in Figure 4 – 8.

Table 5: Analysis of variance for dependent variables in factorial design

For hardness				
Regression	SS	DF	MS	F value
Treatment	2.61	2	1.3	72.98
Residual	0.1072	6	0.0179	
Total	2.72	8		
For Melting point				
Treatment	35.21	2	17.6	46.09
Residual	2.29	6	0.3819	
Total	37.50	8		
For % drug release at 15min				
Treatment	432.38	2	216.19	91.77
Residual	14.13	6	2.36	
Total	446.51	8		

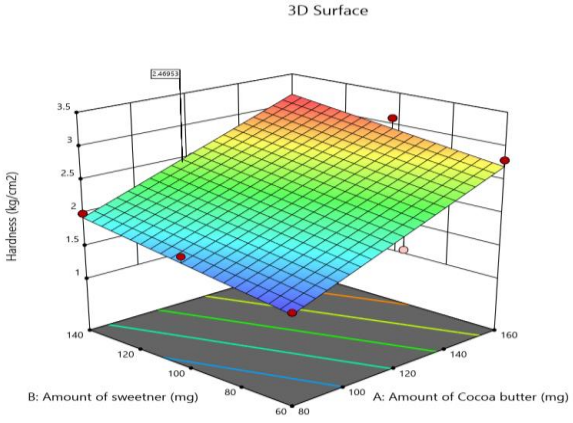

Figure 4: Response surface plot of hardness

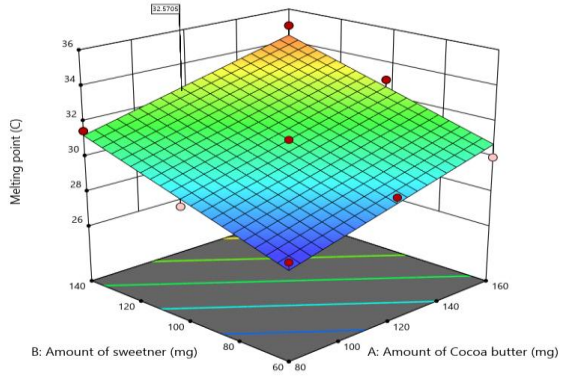

Figure 5: Response surface plot of melting point

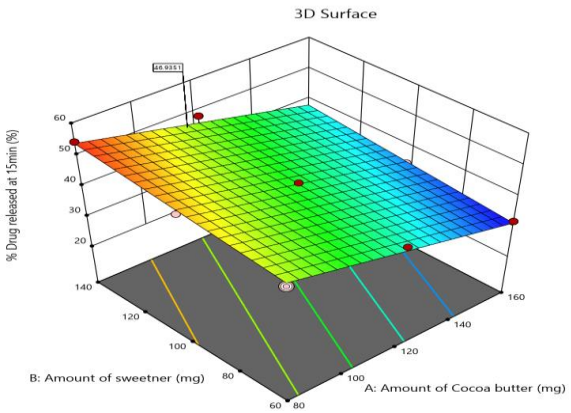

Figure 6: Response surface plot of % drug release at 15min

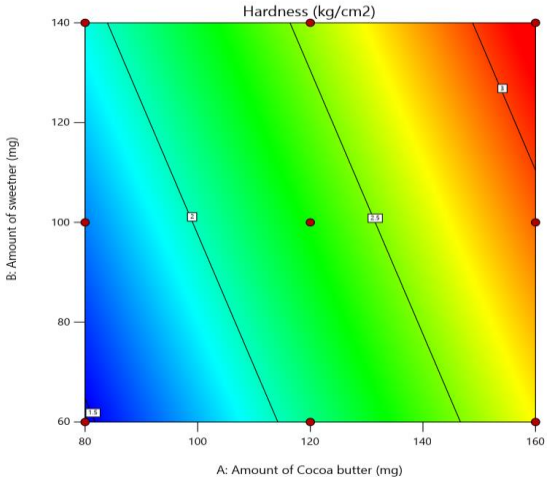

Figure 7: Contour plot of hardness

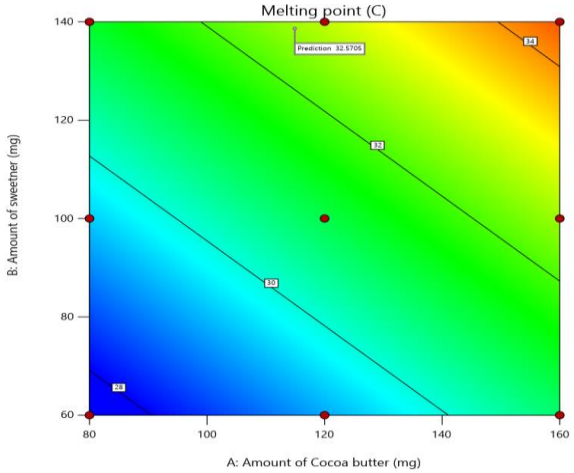

Figure 8: Contour plot of melting point

***In vitro* drug release studies:**

The drug release profiles of the medicated chocolates indicated that the concentration of cocoa butter has significant influence on the drug release profile and were given in Table 6. It is inversely proportional to the release of drug. Drug release profiles of the medicated chocolates were shown in figure and the comparative drug release was shown in Figure 9-12.

Table 6: *In vitro* drug release data of medicated chocolates

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	13.2	17.4	24.5	18.6	20.9	23.4	15.2	16.8	19.3
10	27.4	31.6	38.4	28.7	32.1	35.3	23.2	27.4	29.2
15	46.1	49.2	54.3	40.6	43.1	48.3	32.1	34.4	36.3
20	67.4	74.1	77.2	51.3	56.2	62.1	41.7	46.2	47.5
30	84.3	97.5	99.1	69.4	73.6	76.9	53.6	56.1	58.3
40	98.6			82.7	87.3	89.8	62.4	65.8	69.7
45				96.4	99.2	98.3	71.8	74.7	78.2

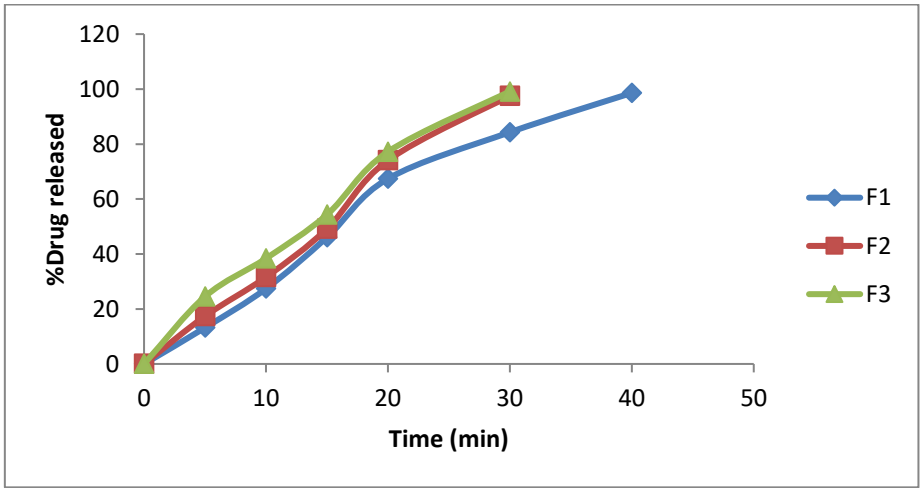

Figure 9: Drug release profile of formulations

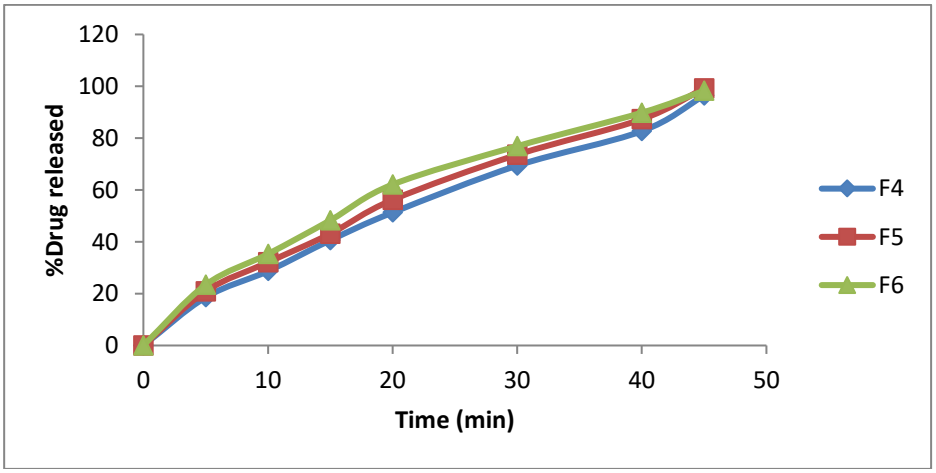

Figure 10: Drug release profile of formulations

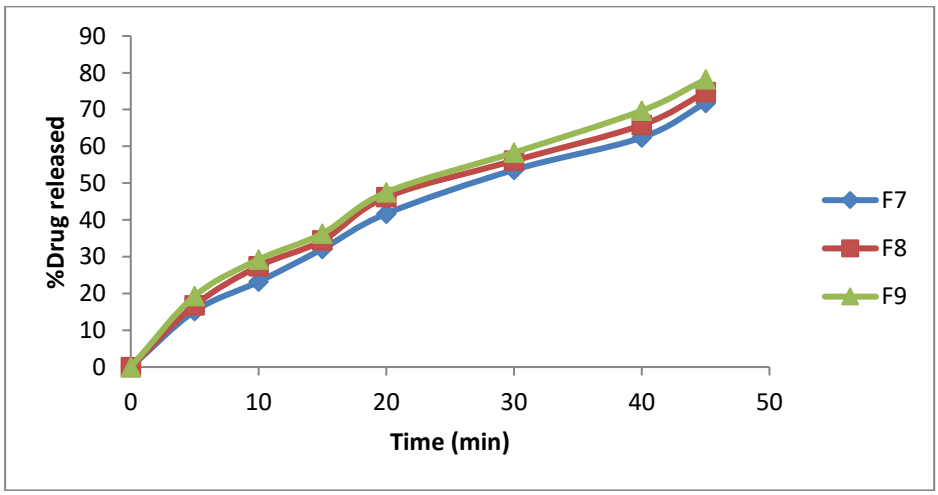

Figure 11: Drug release of formulations

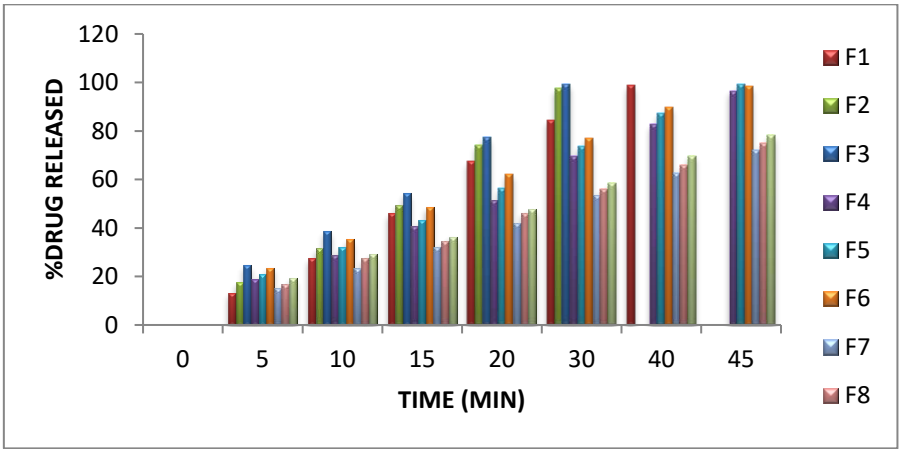

Figure 12: Comparative chart of drug release profiles.

Stability studies:

Stability studies for the optimized formulation were done for 3 months. Formulation was stored in refrigerator and specified temperature (25±5˚C). No degradation was observed in both cases and formulation testing parameters like hardness, melting point and percentage drug released were found to be within ±5%. When compared to the refrigerated condition formulation stored at specified temperature was found to have less hardness with increased release rate. The observations of the stability studies were given in Table 7.

Table 7: Stability study data

S. No	Storage condition	General appearance	Hardness	Melting point	Drug content
1	2-8˚C (Controlled)	No Change	3.1	36˚C	97.2±0.48
2	25±5˚C	Acceptable	2.2	30˚C	95±0.03

CONCLUSION

The aim of the work was development of a formulation to improve pediatric patient compliance. An attempt was made to formulate chocolate dosage form of domperidone. Formulation was optimized using 3^2 factorial design. Batch containing 0.18g cocoa butter, 0.03g cocoa powder, 0.23g mannitol, 0.04g stevia, 0.03g milk powder has been selected to be the best formulation. Drug release from the chocolate if influenced by concentration of cocoa butter and has a negative effect. The work concludes that medicated chocolates can be developed as a prominent dosage form in case of pediatrics to overcome problem of drug administration to them and to decrease level of rejection towards medication.

ACKNOWLEDGEMENTS

The authors are thank full to the educational institutions for providing necessary facilities to carryout the work.

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