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FORMULATION AND EVALUATION OF FEXOFENADINE HYDROCHLORIDE AND PARACETAMOL CHOCOLATE FOR PEDIATRICS

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ABSTRACT

Chocolate is highly sophisticated and much adaptable food that can be combined to create completely different taste and consistency sensations. The objective of the present study is to develop a chocolate formulation of Fexofenadine hydrochloride and Paracetamol for pediatric administration. The formulation consists of developing a chocolate base containing a cocoa powder, cocoa butter, lecithin, and pharmaceutical grade sugar Thereafter drug is incorporated to above prepared chocolate base. Thus the prepared medicated chocolate is evaluated for appearance, moisture content, invitro drug release, blooming test, drug content & drug Excipients compatibility. In-vitro dissolution studies of formulated chocolate were performed by using 0.1N HCL as a dissolution media for Fexofenadine hydrochloride and using 0.1N Na0H as a dissolution media for Paracetamol. Among all six formulations the formulation six (F6) showed complete release of Fexofenadine hydrochloride with 94.52 at the end of 8 hours, Paracetamol with 98.11 at the end of 4 hours. The drug release from the chocolate shows First order release kinetics and diffusion mechanism.

KEYWORDS: Medicated Chocolate, Pediatrics, Chocolate formulation.

INTRODUCTION

Chocolate is highly sophisticated and much infinitely adaptable food that can be combined to create completely different taste and consistency sensations. Chocolate is an anhydrous medium resistant to microbial growth and hydrolysis for water-sensitive active agents.[1,2] Chocolate abundantly contains compounds such as saturated fat, polyphenols, sterols, di and triterpenes, aliphatic alcohols, methylxanthines, flavanols, antioxidants Cocoa is the main

ingredient of chocolate and it is loaded in polyphenols. Research studies facilitate that high intake of dietary flavonoids, a subgroup of polyphenols, may reduce the risk of coronary heart disease.[3,5]

Anti oxidants help cell resist damage caused by free radicals formed during bodily processes, such as breathing, and from environmental contaminants, like cigarette smoke. The lack of antioxidants creates damage to our body by free radicals. For example, an increase in oxidation can cause low-density lipoprotein (LDL), also known as "bad" cholesterol, to form plaque on the artery walls.[4,6]

Flavanols are mainly found in cocoa and chocolate. In addition to having antioxidant qualities, research shows that flavanols have other potential influences on vascular health, such as lowering blood pressure, improving blood flow to the brain and heart, and making blood platelets less sticky and able to clot. Though chocolate has hundreds of naturally occurring chemicals one good example is that certain substances in chocolate have been shown to help our body produce chemical known as “serotonin”. It makes feel relaxed.[7,8]
Taste is defined as “the sensation of flavor perceived in the mouth on contact with substance”. Chocolate containing the drug in suitable quantity is known as medicated chocolate Basically there are four types of taste modalities, salty, sour, bitter, sweet through the combination of these elements we can detect the “flavors” Children’s tastes sensation is much differ than adults infants and more over children have a preference for sweet-tasting substance. Chocolate have been shown to help our body produce chemical known as “Serotonin”. It makes feel relaxed.

MATERIALS AND METHOD

Paracetamol and Fexofenadine hydrochloride, lecithin and pharmaceutical grade sugar are mainly used for the preparation of chocolates. Paracetamol is obtained from Accord labs Mumbai, Fexofenadine hydrochloride, soya lecithin, and cocoa butter was obtained from Yarrow chemicals Mumbai, Cocoa powder was obtained from Amrut international Ahmadabad, Gujarat.

Preparation of chocolate base

The sugar syrup is initially prepared by heating sugar (pharmaceutical grade) and water in a beaker using heating mantle at 50^0C for 4-5 minutes. The cocoa base is prepared by melting the cocoa butter in a beaker for 2 minutes and adding the above prepared sugar syrup and

cocoa powder to it. This mixture is cooled up to semisolid consistency and adding a flavoring agent.

Method of preparation of chocolate

Oven was set at 50^0C. Then prepared chocolate base was melted until it becomes a free flowing liquid. After that required quantity of Active pharmaceutical ingredients was added. Then it was stirred well with the help of magnetic stirring for 10 minutes to ensure uniform mixing. Then we poured the above mixture in a polycarbonate set mould and cooled for 15 minutes till it become solid.

Table No. 1: Composition of Medicated chocolate

Ingredients	Category	F1	F2	F3	F4	F5	F6
Fexofenadine hydrochloride	Anti-pyretic	0.03gm	0.03gm	0.03gm	0.03gm	0.03gm	0.03gm
Paracetamol	Anti-allergic	0.24gm	0.24gm	0.24gm	0.24gm	0.24gm	0.24gm
Lecithin	Emulsifier	0.75gm	0.25gm	0.50gm	0.75gm	0.75gm	0.50gm
Cocoa Butter	Solidifying agent	0.85gm	1gm	1gm	1gm	0.50gm	0.75gm
Cocoa powder	Principal ingredient	2.5gm	2.5gm	2.5gm	2.5gm	2.5gm	2.5gm
Pharmaceutical grade Sugar	Sweetening agent	1.8gm	2.0gm	1.8gm	1.5gm	2.0gm	2.05gm
Flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preformulation studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with Excipients. The overall objective of pre formulation testing is to generate information useful to the formulator in developing stable, efficacious and safe dosage form. Hence Preformulation studies were carried out on the obtained samples of drug for identification and compatibility studies.

Solubility

Paracetamol and Fexofenadine hydrochloride both drugs are freely soluble in Methanol

Identification of Drug

The obtained sample was examined by infrared absorption spectral analysis and was compared with the reference standard IR spectrum of Paracetamol and Fexofenadine hydrochloride.

Method

IR Spectra of drug and drug-Excipients blends were recorded on an IR spectrophotometer (Shimadzu Corporation, Japan) in the range of 4000-400Cm^{-1} using potassium bromide discs.

Compatibility studies

The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. Incompatibility between drugs and Excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and efficacy in development of dosage form.

The compatibility between pure drug and Excipients were detected by FTIR spectra obtained by Brucker, Germany. The potassium bromide pellets were prepared by using pellet press. For the preparation of pellets, powder sample were ground together in a mortar with 5 times quantity of KBr then finely grounded powder was introduced into a stainless steel die. The powder was pressed in the die between polished steel anvils at a pressure of 50 pounds. Obtained spectra's were recorded over the wave number of 4000^{-1} to 400cm^{-1}

Evaluation of chocolate

General appearance

The general appearance of a chocolate formulation is determined by observing its visual identity and overall "elegance" is necessary for consumer acceptance and for observing trouble free manufacturing.

Table No. 2: General appearance

Serial no:	Characteristics	Result
1.	Color	Brown
2.	Odor	Pleasant
3.	Taste	Sweet
4.	Surface texture	Smooth, silky

Dimensions

Dimension of the chocolate was measured by using vernier's calipers.

Viscosity determination of chocolate base

The viscosity was determined by using Brookfield rotational viscometer where the spindle was rotated at 50rpm and chocolate base was heated at 30^{0}c before measurements were taken.

Taste, texture and mouth feel characteristics measurement

Taste, texture and mouth feel characteristics of chocolate is evaluated by taking panel of 20 human volunteers

Table No.3: Taste, Texture and mouth feel characteristics sense

Serial. no	Characters	Criteria	Results
1.	Appearance	Glossy in appearance	Acceptable
2.	Smell	Chocolaty smell with flavor, no chemical smell	Acceptable
3.	Taste	Chocolaty, good in taste	Acceptable
4.	Texture	Creamy and silky, melts in mouth	Acceptable

Moisture content determination

Moisture content determination was determined by using Desicator

This test was carried out to check the moisture present in the chocolate at dry condition. The prepared chocolate formulation were weighed accurately and kept in a desicator containing anhydrous silica gel. After 24hrs, the formulations were taken out weighed and % Moisture Absorption was calculated by using formula.

$$\% \textbf{ Moisture Loss} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\text{Initial weight}} \times \textbf{100}$$

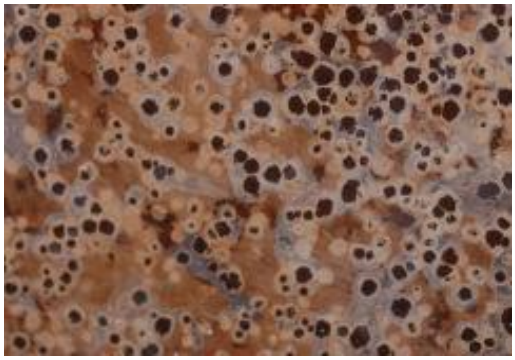
Blooming test

Blooming test of chocolate is two types (1) Sugar bloom

(2) Fat bloom

Sugar bloom

It is caused by contact of the chocolate with the moisture Chocolate is composed of cocoa beans and sugar, and sometimes flavor and lecithin. While you may not see the sugar crystals present in chocolate they are too small to see. Water comes in contact with the chocolate, dissolves the sugar present on the surface of the chocolate. As the water dries, the dissolved sugar crystallizes and precipitates the surface of the chocolate. The resulting small sugar crystals give the chocolate layer a dusty appearance. Storage at the constant temperature delay the of the condensation of the chocolate and appearance of sugar bloom.



Fat bloom

Fat bloom appears as light color spots on the chocolate. As the name says, the bloom is composed of fat, in this case the naturally occurring fat that comes from the cacao bean - cocoa butter. A soft white layer will appear gives bland look.

(1)Sample was subjected to 40^0c for 8 hours, and Temperature is shifted for 20^0c. A test sample was observed, after the step of 20^0c for 8 hours whether bloom has taken place or not.

Drug content determination

Drug content of a medicated chocolate was determined by using U.V. spectrophotometer.

Method of sample preparation for Paracetamol

The Prepared medicated chocolate, sample was taken in 50ml beaker, mixed in 10ml of ethanol, the obtained product is subjected for sonification by using sonicator to ensure size reduction and proper mixing of the ingredients. Then the obtained product is subjected for ultra centrifugation at 2500rpm for 20 min to leave two layers. The upper layer contains the dissolved drug and the lower layer contains a solid layer of chocolate base. The supernatant upper layer is filtered through Whatmann filter paper to remove the traces of chocolate base and analyzed using U.V spectrophotometer against blank.

Method of sample preparation for Fexofenadine hydrochloride

The Prepared medicated chocolate, sample was taken in 50ml beaker, mixed in 10ml of ethanol, the obtained product is subjected for sonification by using sonicator to ensure size reduction and proper mixing of the ingredients. Then the obtained product is subjected for ultra centrifugation at 2500rpm for 20 min to leave two layers. The upper layer contains the dissolved drug and the lower layer contains a solid layer of chocolate base. The supernatant upper layer is filtered through Whatmann filter paper to remove the traces of chocolate base and analyzed using U.V spectrophotometer against blank.

In vitro drug Release

Invitro drug release for Paracetamol

In vitro drug release study of chocolate formulation was performed in USP dissolution apparatus Type 1(Basket), using 0.1N HCL as a dissolution media for Paracetamol. The bowls of the dissolution apparatus was filled with 900ml of 0.1NHCL was placed and allowed to attain a temperature of 37±0.5^{0}c and 50rpm. A chocolate formulation was placed in a basket. At a pre determined time interval_i.e._10min, 20min, 30min up to 4hours 10mlof sample was withdrawn at a predetermined time intervals and volume was replaced with equal quantity of fresh medium. The collected samples were filtered and analyzed by U.V. spectrophotometer. The concentration of Paracetamol was calculated using slope of calibration curve and cumulative percentage drug release was calculated.

In vitro drug release for Fexofenadine hydrochloride

In vitro drug release study of chocolate formulation was performed in USP dissolution apparatus Type 1(Basket), using 0.1N Na0H as a dissolution media for Fexofenadine hydrochloride. The bowls of the dissolution apparatus was filled with 0.1NNaoH was placed and allowed to attain a temperature of 37±0.5^{0}c and 50rpm. A chocolate formulation was placed in a basket. At a pre determined time interval_i.e.1hr, 2hr, and 3hr, up to 8hrs. 10mlof sample was withdrawn at a predetermined time intervals and volume was replaced with equal quantity of fresh medium. The collected samples were filtered and analyzed by U.V. spectrophotometer. The concentration of Fexofenadine hydrochloride was calculated using slope of calibration curve and cumulative percentage drug release was calculated.

RESULTS AND DISCUSSION

The IR Spectrum of pure drugs was found to be similar to that of standard spectra's of Paracetamol and Fexofenadine hydrochloride. The spectra's of paracetamol and Fexofenadine hydrochloride shows the following functional groups at their frequencies shown in

Functional groups	Frequencies for Paracetamol	Frequencies for Fexofenadine Hydrochloride
C=C	3574.88 3783.53	1448.42 1490.78
C-H stretch (Aromatic)	3298.44	2934.92 3063.08
C-H stretch	2670.63	2671.67
O-H stretch	1169.01 1258.60	1166.10 1279.58
Tertiary Alcohol	1442.02	1403.08
C-N stretch	1068.58 1015.13	1068.50

Compatibility studies of Paracetamol and Fexofenadine hydrochloride with Excipients were carried out prior to the formulation of medicated chocolate. IR spectra of pure drug and Excipients were taken, which are depicted in figure No: 3 and figure No: 4. All the characteristic peaks of Paracetamol and Fexofenadine hydrochloride were present in spectra at respective wavelengths. Indicating that compatibility between drug and Excipients shows that there was no significant change in the chemical integrity of the drug.

General appearance of prepared formulations are rectangle in shape with length, width and height of 3.5, 2.3, 1.8 cms respectively Taste, texture& mouth feel characteristics of chocolate base was determined by taking panel of 20 human volunteers and it was found to be acceptable.

Viscosity of chocolate base was determined by Brookfield rotational digital viscometer and results were shown in table

Table No.4: Viscosity determination of Chocolate formulations

S.NO	Formulation code	Viscosity of Formulation
1	F1	58,264cps
2	F2	61,562cps
3	F3	60,152cps
4	F4	61,456cps
5	F5	60,126cps
6	F6	62,236cps

Moisture content determination was done by using Desicator and is calculated by using formula and the results are shown in Table No: 4.

Table No.5: Percentage Moisture content determination

S.No	Formulation code	%Moisture Loss
1	F1	5.67
2	F2	1.32
3	F3	3.45
4	F4	1.66
5	F5	1.99
6	F6	4.11

No blooming was observed in any formulation of chocolate For Fexofenadine hydrochloride chocolate drug content was found to be 94.52mg and for Paracetamol medicated chocolate drug content was found to be 98.11mg.

Invitro drug release

Table No. 6: Percentage cumulative drug release profile of Paracetamol

S.NO	TIME (min)	% CUMULATIVE DRUG RELEASE					
		F1	F2	F3	F4	F5	F6
1	10	26.42	38.72	35.04	53.00	43.60	11.03
2	20	33.06	40.88	37.94	54.43	46.83	14.05
3	30	35.299	45.06	38.31	56.87	48.10	18.05
4	40	39.87	47.42	42.32	58.19	49.03	22.56
5	50	46.54	51.99	49.22	61.88	51.90	28.56
6	60	48.80	55.12	53.71	64.83	54.42	31.06
7	90	51.07	60.46	58.39	69.16	60.54	44.56
8	120	58.86	62.84	63.17	72.00	65.90	52.63
9	150	65.5	63.57	65.65	77.21	66.85	62.55
10	180	68.9	65.28	68.13	79.29	71.22	75.62
11	210	69.00	66.89	68.70	82.15	72.18	82.64
12	240	72.39	67.74	69.12	85.24	76.65	94.68

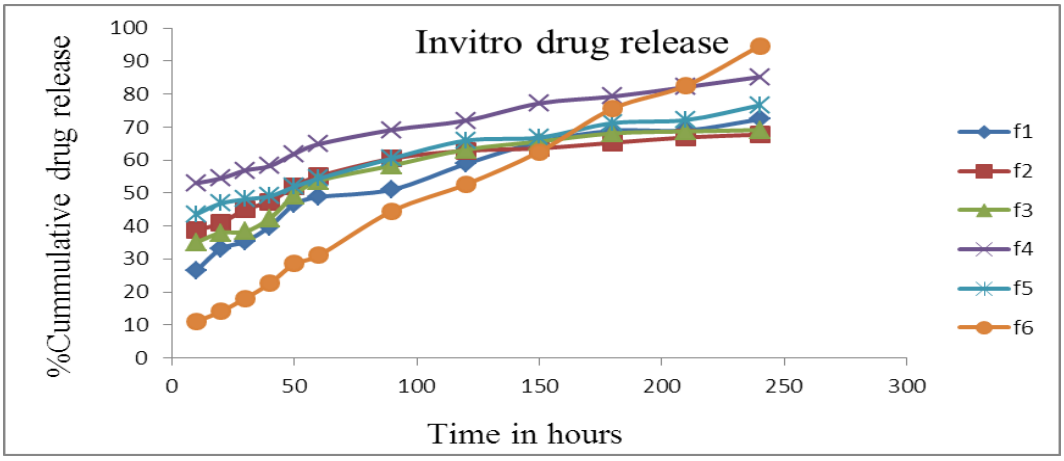


Figure No: 1 Invitro drug release plot of Paracetamol for all formulations.

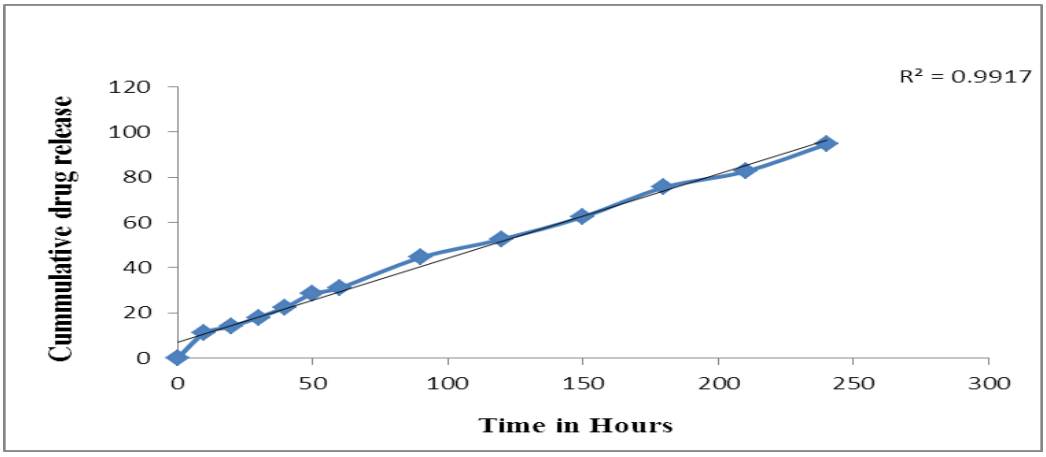


Figure No. 2: Invitro drug release plot for best Formulation (F6)

TableNo.7: Percentage cumulative drug release profile of Fexofenadine Hydrochloride

S.NO	TIME (min)	%CUMULATIVE DRUG RELEASE					
		F1	F2	F3	F4	F5	F6
1	1	28.72	31.83	38.11	33.74	27.29	52.54
2	2	37.60	40.27	51.91	39.03	30.73	62.68
3	3	39.85	43.23	60.66	49.98	45.55	71.27
4	4	47.64	57.74	63.48	58.29	47.88	76.98
5	5	51.02	63.96	73.43	64.10	64.99	82.83
6	6	61.03	69.64	83.12	70.98	70.75	88.55
7	7	69.40	77.70	85.64	74.65	76.51	91.54
8	8	75.00	86.75	86.96	86.22	82.11	94.52

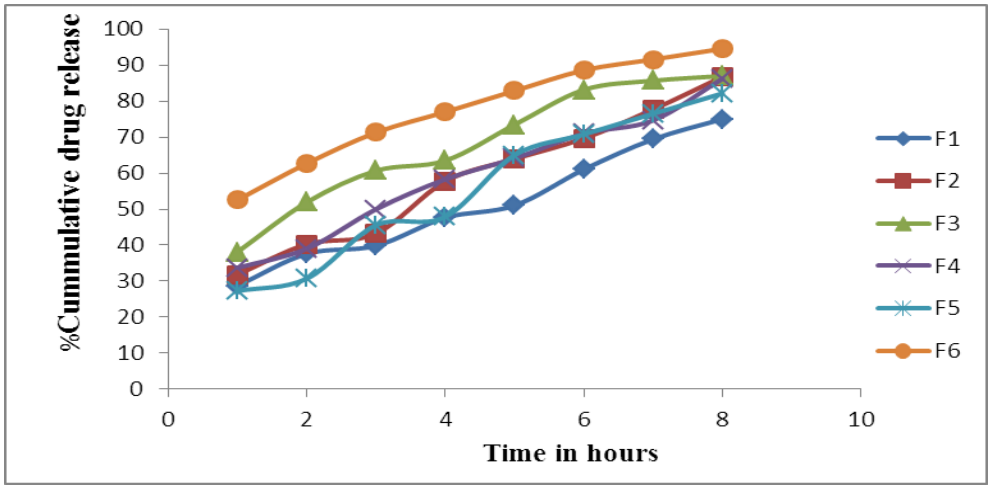


Figure No.3: Invitro drug release plot of Fexofenadine hydrochloride for all formulations

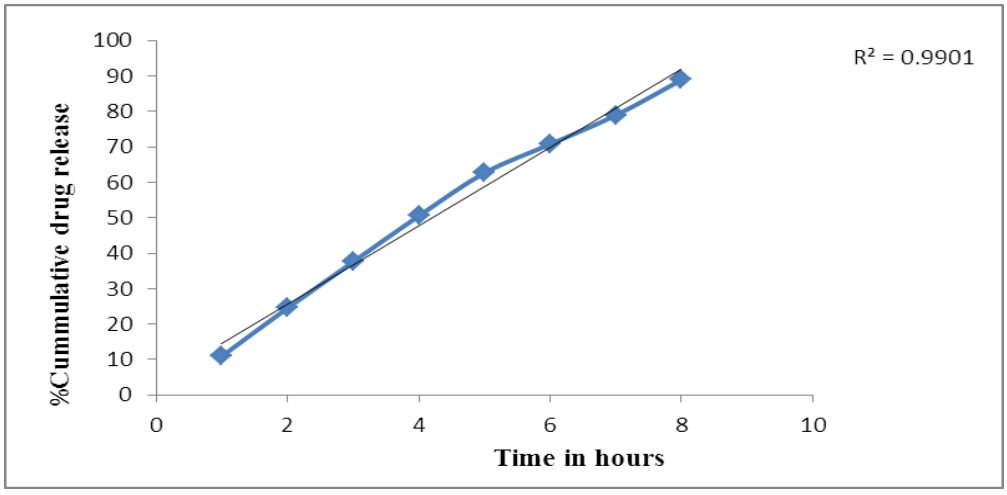


Figure No: 4 Invitro drug release for best formulation (F6)

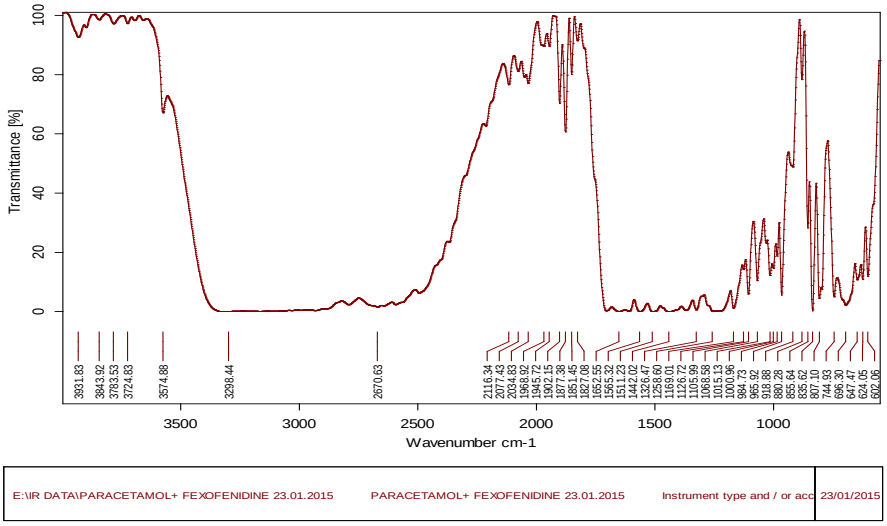


Figure No.5: IR spectra of Paracetamol with Fexofenadine hydrochloride.

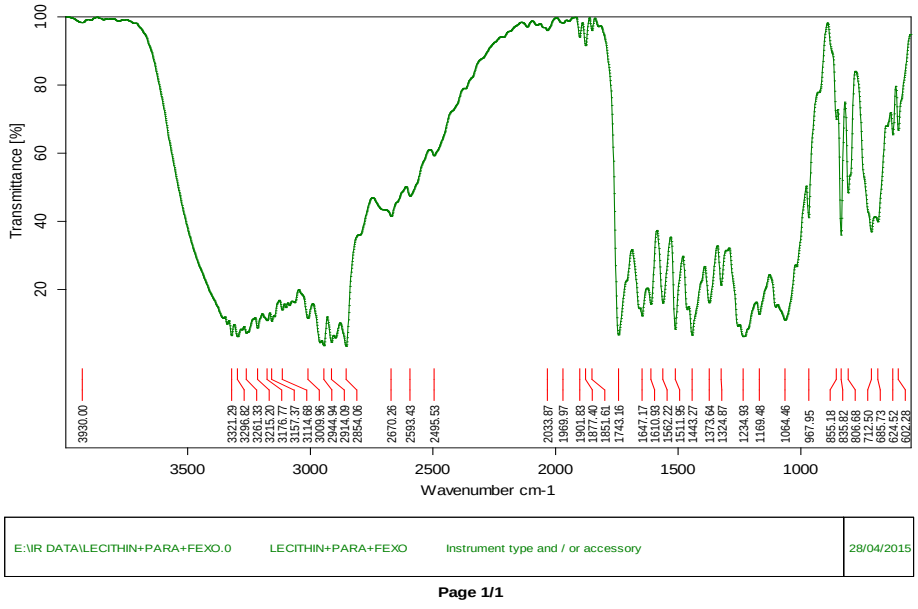


Figure No.6: IR spectra of Lecithin with Paracetamol and Fexofenadine hydrochloride

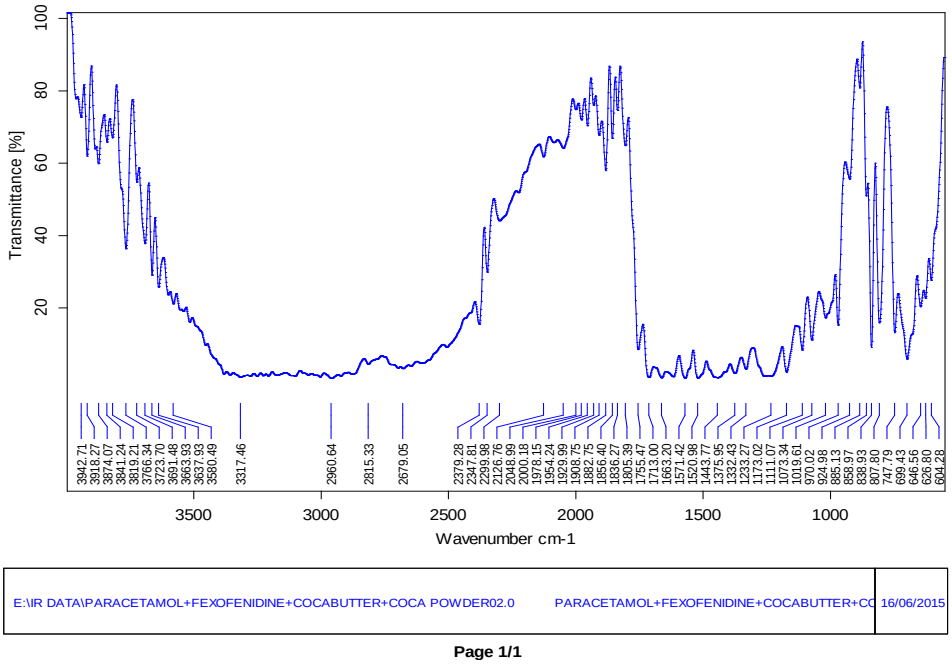


Figure No.7: IR spectra of Paracetamol with Fexofenadine hydrochloride, cocoa powder and cocoa butter

Table No.8: Calibration curve data for Paracetamol at 257nm

S.No	Concentration in µg/ml	Absorbance at 257nm
1	0	0
2	5	0.143
3	10	0.274
4	15	0.421
5	20	0.564
6	25	0.695

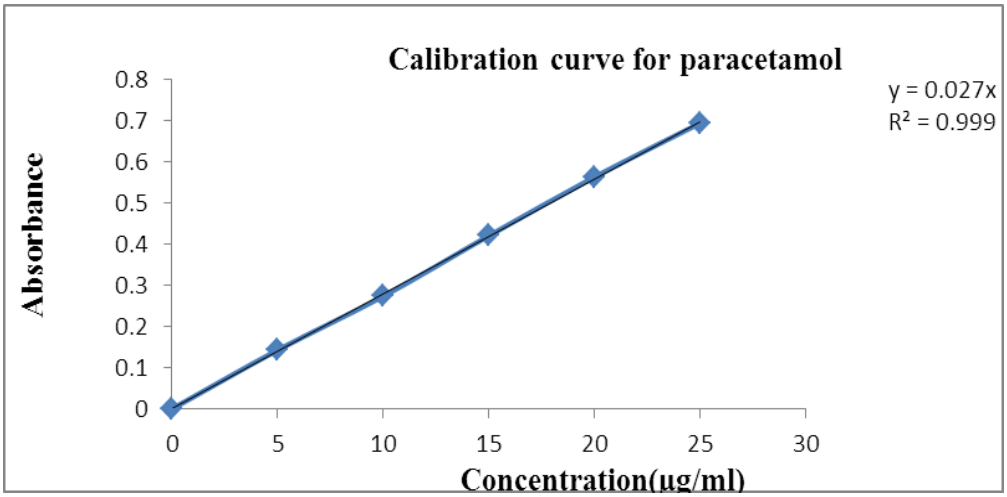


Figure No. 8: Calibration curve plot for Paracetamol

Table No.9: Calibration curve data for Fexofenadine hydrochloride at 257nm

S.No	Concentration in µg/ml	Absorbance at 257nm
1	0	0
2	5	0.120
3	10	0.241
4	15	0.353
5	20	0.472
6	25	0.591
7	30	0.715
8	35	0.832
9	40	0.951

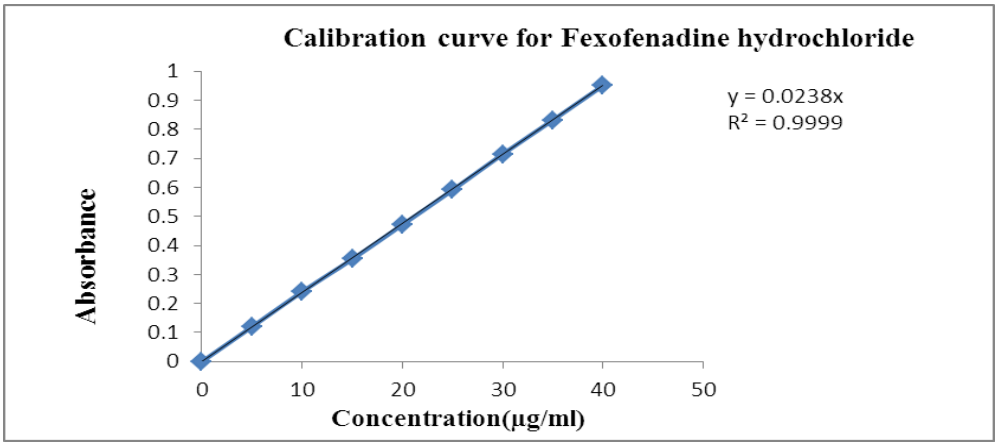


Figure No. 9: Calibration plot for fexofenadine hydrochloride.

Release kinetics for all formulations

Invitro release data was subjected to zero order, first order, Higuchi and krosmeyer-peppas models in order to establish the drug release mechanism and kinetics of the drug release from the prepared medicated chocolate.

When the data was subjected to zero order and first order kinetics model, a linear relationship was observed with R^2 values for zero order model as compared to first order model and it suggested that the formulations followed first order release.

Higuchis model was applied to the in-vitro release data, linearity was obtained with high R^2 values suggested that the drug release from the chocolate followed diffusion mechanism.

In order to define perfect model which will represent a better fit for in-vitro release data, Korsemeyers-Peppas model was applied which will define the exact mechanism. Good linearity with high R^2 values was observed with this model. The value of 'n' obtained for all

the formulation was ›0.45 suggesting that the drug release follows first order fiction diffusion.

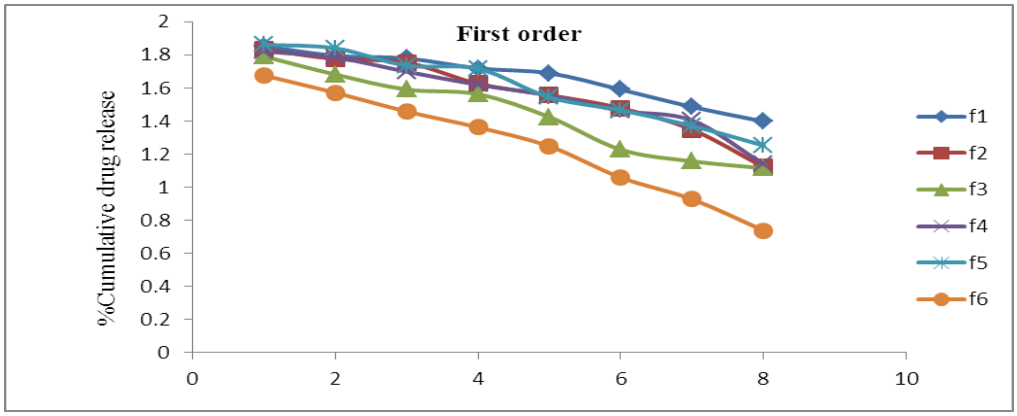


Figure No.10: First order Invitro release plot for Fexofenadine hydrochloride

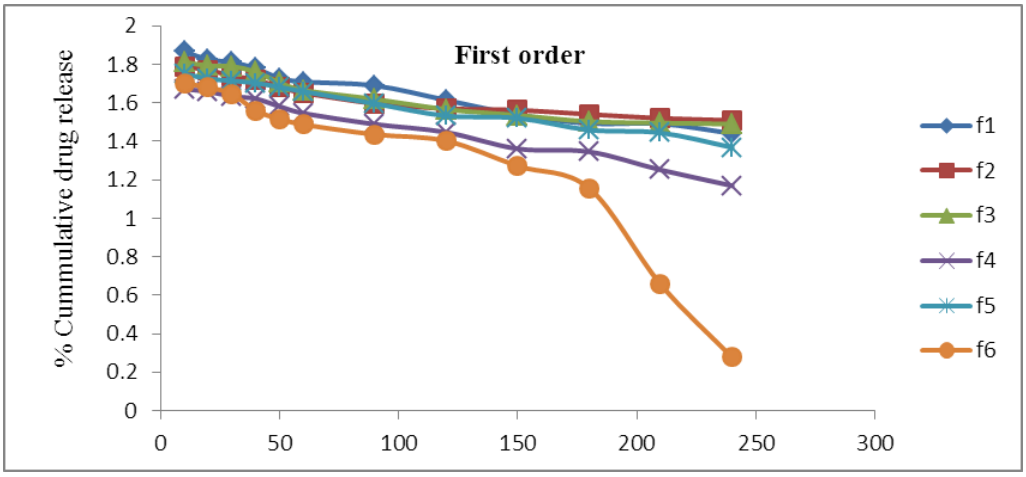


Figure No.11 First order Invitro release plot for Paracetamol

Time Vs LOG % CDR Retained First order kinetics of F1-F6

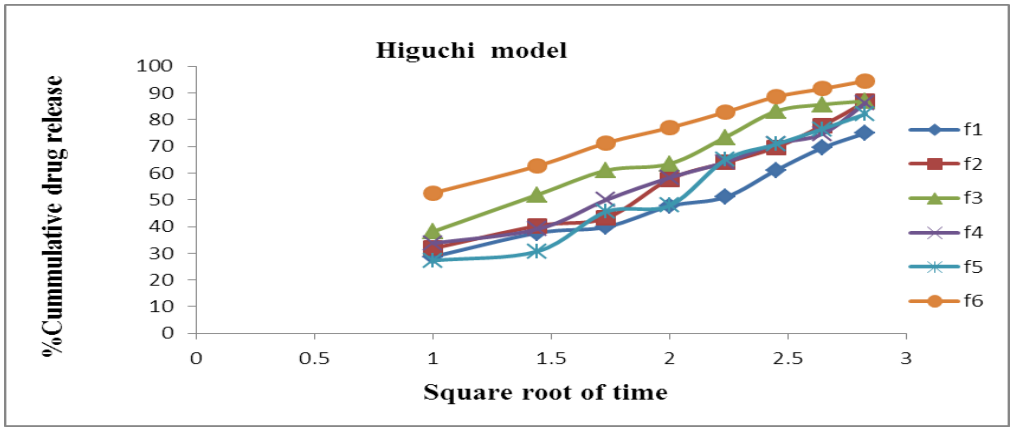


Figure No.12: Higuchi plot for Fexofenadine Hydrochloride

Square root of time Vs % CDR Higuchi Release Mechanism of F1-F6

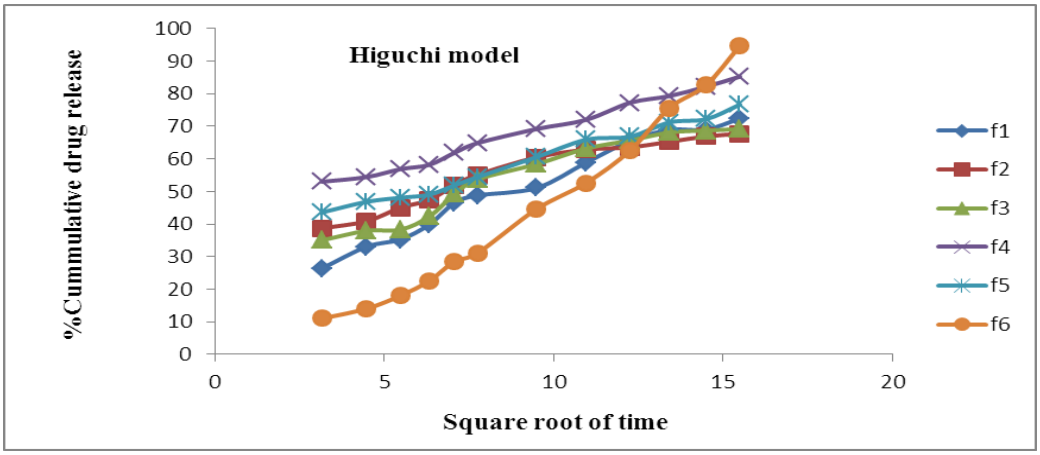


Figure No.13: Higuchi plot for Paracetamol

Square root of time Vs % CDR Higuchi Release Mechanism of F1-F6

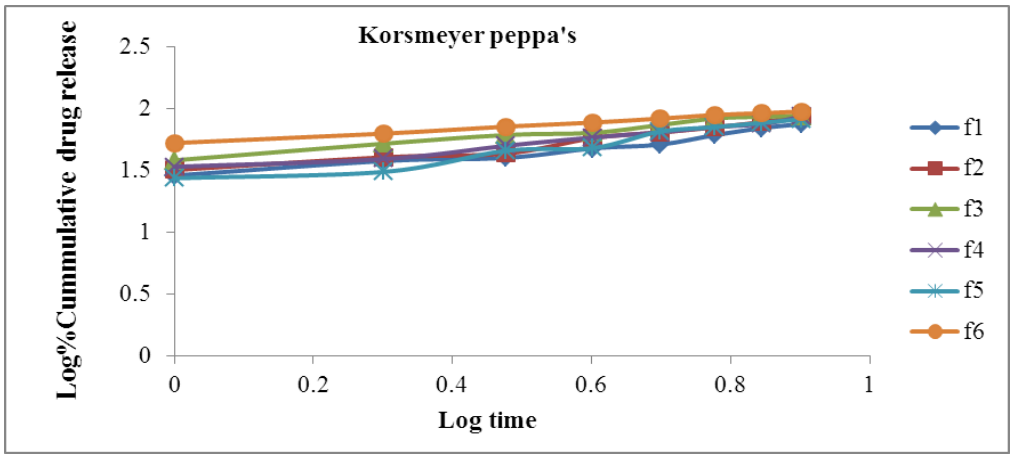


Figure No.14: Korsmeyer peppa's plot for Fexofenadine Hydrochloride

Time Vs Log % CDR Korsmeyer peppa's Release Mechanism of F1-F6

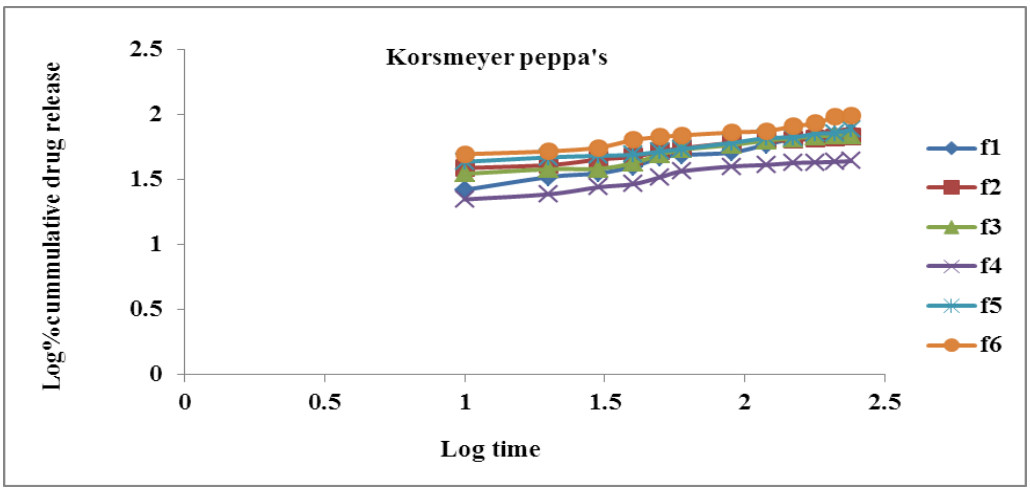


Figure No.15: Korsmeyer peppa's plot for Paracetamol

Time Vs Log % CDR Korsmeyer peppa's Release Mechanism of F1-F6

Table No.10: Release Kinetics Data of the Formulations F1-F6 for Paracetamol

Formulation Code	Zero Order R2	First order R2	Higuchi's R2	Korsmeyer peppa's	
				n	R2
1.	0.922	0.968	0.980	0.326	0.988
2.	0.848	0.895	0.942	0.195	0.973
3.	0.868	0.915	0.946	0.250	0.953
4.	0.970	0.991	0.993	0.236	0.956
5.	0.965	0.987	0.988	0.189	0.957
6.	0.996	0.867	0.981	0.218	0.959

Table No.11: Release Kinetics Data of the Formulations F1-F6 for Fexofenadine hydrochloride

Formulation Code	Zero Order R2	First order R2	Higuchi's R2	Korsmeyer peppa's	
				n	R^2
1.	0.985	0.95	0.952	0.456	0.949
2.	0.989	0.940	0.969	0.489	0.691
3.	0.953	0.973	0.982	0.405	0.987
4.	0.989	0.937	0.977	0.456	0.972
5.	0.974	0.973	0.962	0.578	0.950
6.	0.990	0.986	0.995	0.289	0.998

CONCLUSION

Chocolate formulation serves as a favorable for masking the unpleasant flavor of a majority of active ingredients and imparts a smooth, silky and creamy texture to the compositions of active ingredients. The commercial acceptance of chocolate form of pharmaceutical (or) nutraceutical agents is not favored due to their formulation but by controlling particle size of the pharmaceutical active ingredient it can be successfully achieved. Thus chocolate drug delivery provides a suitable, palatable source for delivery of medicaments through oral route.

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