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Research Article

Design and Fabrication of Medicated Chocolate Formulation by Chocolate Drug Delivery System.

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ABSTRACT
The objective of this study is to design and fabricate Chlorpheniramine Maleate chocolate formulation by chocolate drug delivery system. Chlorpheniramine Maleate binds to histamine H1 receptor. This blocks action of endogenous histamine, which subsequently leads to temporary relief of negative symptoms brought on by histamine. Chocolate is a range of products derived from cocoa (cacao), mixed with fat (i.e., cocoa butter) and finely powdered sugar to produce a solid confectionery. Medicated chocolate formulation is widely used for pediatric administration and increases patient compliance. Chlorpheniramine Maleate chocolate formulation is prepared to improve patient compliance. Chocolates were formulated (F1-F3) with total fat of 25-35 % (w/w) from cocoa liquor and cocoa butter with more than 34% total cocoa, composition as specified for dark chocolate, lecithin, sweetening agents. The prepared chocolate formulations were evaluated for general appearance, drug content, *In vitro* drug release and DSC and FTIR, moisture content and blooming tests. F1 formulation releases complete drug within 60min. The results indicate that the formulation has no drug excipient interactions and there was no degradation in drug, it is stable during chocolate formulation preparation.

KEYWORDS
Chlorpheniramine Maleate, chocolate, medicated chocolate, Invitro drug release.

1. INTRODUCTION

A Trans mucosal route includes mucosal linings along nasal, vaginal, rectal and oral cavities[1]. The advantages of Trans mucosal routes[2] includes significant reduction in dose related side effects, provides direct entry of drug into systemic circulation. Drug absorption can be terminated in case of emergency. It offers rapid cellular recovery following local stress or damage, ability to withstand environmental extremes like change in pH, temperature etc. It is a sustained drug delivery and has the potential for delivery of peptide molecules unsuitable for the oral route. Chocolate is a range of products derived from cocoa (cacao), mixed with fat (i.e., cocoa butter) and finely powdered sugar to produce a solid confectionery.

There are a number of ingredients in chocolate; the most notable of these are caffeine and theobromine. These two chemicals are closely related and are found in all cocoa beans. It is a typically sweet, usually brown, food preparation of Theobroma cacao seeds, roasted and ground, often flavored, as with vanilla. Chocolate is also an anhydrous medium and is therefore resistant to microbial growth and to hydrolysis of water-sensitive active agents. Medicated chocolate is prepared by using chocolate base and drug is incorporated in to prepared chocolate base[3].

As drug is incorporated within the chocolate and the drug is released from the chocolate, it is called as Chocolate drug delivery system. It has advantages that include possible bypass of first-pass effects and avoidance of presystemic elimination within the GI tract. Chocolate is also an anhydrous medium and is therefore resistant to microbial growth and to hydrolysis of water-sensitive active agents. Chocolate is well-suited as a vehicle for delivering active agents in many aspects.

The aim of present study is to design and formulate a chocolate formulation as a drug delivery system of an first generation alkyl amine Anti-histamine drug Chlorpheniramine Maleate with following objective,

- To improve patient compliance.
- To study the kinetic profile of drug release.
- Comparison of release profiles of different composition of excipients in formulations.

In the present study, chocolate drug delivery system through the oral route, especially the buccal route was utilized as a platform for Histamine receptors antagonists; hence it is possible to realize local effect drug administration.

In local effect, the aim is to achieve a site specific release of drug on mucosa, whereas the systemic effect involves drug absorption through mucosal barrier to reach systemic circulation. The buccal mucosa is highly vascularized and presents a reduced enzymatic activity when compared to gastro intestinal, rectal and nasal mucosa[4].

2. MATERIALS AND METHODS

2.1. Materials

Chlorpheniramine Maleate, Lecithin, Pharmaceutical grade sugar was purchased from Nihal traders (Hyderabad, Telangana, India.), AET Labs (Hyderabad, Telangana, India.), respectively Cocoa Butter was purchased from AET Labs (India), Cocoa Powder was purchased from Weikfield India. All the other chemicals like Dicalcium Phosphate, Mango flavor, Pine apple flavor used are of analytical grade.

2.2. Methods

2.2.1. Formulation of chocolate Base

Chocolates were formulated with total fat of 25-35 % (w/w) from cocoa liquor and cocoa butter with more than 34% total cocoa, composition as specified for dark chocolate (European Commission Directive, 2000; Codex Revised Standard, 2003) (Table 1) (Afoakwa,2010).

2.2.1.1. Method of preparation

Oven was set to 50^0 C. In a beaker, sugar and water was taken and kept in the oven for 4-5 min and syrup was prepared. Then cocoa butter was taken and kept in the beaker in the oven for 1min. Then sugar syrup was removed from the oven, and cocoa powder was added and mixed well. Careful attention is paid to the chocolate manufacturing process to ensure that the temperature of the mixture is not too high. Then above mixture of chocolate base was cooled up to semisolid consistency and then flavor was added. Chocolate base preparation is shown in the Table 4.

2.2.3. Formulation of medicated chocolate

Chocolate squares containing drug in appropriate quantity is known as medicated chocolate.

2.2.3.1. Method of preparation

Oven was set at 50°C. Then chocolate base was melted till it becomes free flowing liquid. After above step; required quantity of drug was added. Then whole mass was stirred well with the help of magnetic stirrer to ensure uniform mixing. Then we poured the above mixture in a polycarbonate set mould and refrigerated for 15 min till it become solid.

Medicated chocolates were prepared in the three formulations. In the I formulation, a batch of ten units were prepared where each single unit possess Chlorpheniramine Maleate drug, Cocoa Powder, Cocoa Butter, Lecithin and Pharmaceutical Grade Sugar were mixed uniformly in a proper order, in order to get an medicated chocolate formulation.

But a problem occurred in the sense of odor. While preparing the formulation, the Cocoa powder odor was very much dominating and was strong to smell and while evaluating the formulation, a pungent smell caused by Lecithin was also observed. So, a flavor was added in order to reduce the strong smell and pungent smell of Cocoa powder and Lecithin. The formulation was shown in the table 1. In the II formulation, a batch of ten units were prepared where each single unit possess Chlorpheniramine Maleate drug, Cocoa Powder, Cocoa Butter, Lecithin, Pharmaceutical Grade Sugar and Pine apple flavor were mixed evenly in a proper order, in order to get an medicated chocolate formulation. Here in this formulation, additionally flavor was added to the formulation in order to mask the strong odor and pungent smell of Cocoa powder and Lecithin. So, improper solidification of formulation while collecting the prepared medicated chocolate from the molds and chances of breakage of formulation and there by improper shaping of the formulation.

So, in order to overcome this problem, an adsorbent Dicalcium phosphate was added to the formulation. The formulation was shown in the table 2. In the III formulation, a batch of ten formulations were prepared where each single unit possess Chlorpheniramine Maleate drug,

Cocoa Powder, Cocoa Butter, Lecithin, Pharmaceutical Grade Sugar, Mango flavor and Dicalcium Phosphate were mixed evenly in a proper order, in order to get a medicated chocolate formulation. The formulation was shown in the table 3. Additionally Dicalcium Phosphate was added to the formulation in order to overcome in proper solidification of formulation while collecting the prepared medicated chocolate from the molds. There is a change in the type of flavor used, which is a Mango flavor in formulation III and Pine apple flavor was used in formulation II. Pine apple flavor containing formulation was very much acceptable when compared to Mango flavor. The Pine apple flavor acceptance is very good, in the sense of odor and taste.

2.3. Evaluation Parameters[5]

2.3.1. Evaluation of Chocolate Base

2.3.1.1. Taste, texture and mouth feel characteristics assessment

Taste, texture & mouth feel characteristics of chocolate were evaluated by taking panel of 10 human volunteers on a rating scale of 1-5.

2.4. Evaluation of Medicated Chocolates

2.4.1. General Appearance

The general appearance of a chocolate formulation, its visual identity and overall "elegance," is essential.

(i) For Consumer acceptance

(ii) For control of lot to lot uniformity and

(iii) For monitoring trouble free manufacturing.

The control of the general appearance of a chocolate involve the measurement of number of attributes such as chocolate's color, presence or absence of an odor, taste, surface texture and physical flaws.

2.5. Evaluation of Physico-Chemical Properties

2.5.1. Drug excipients compatibility studies

Drug excipient compatibility tests like DSC and FTIR are performed for both pure drug as well as Medicated Chocolate i.e., Chocolate base with Chlorpheniramine Maleate and other excipients used in the formulation.

2.5.1.1. Thickness

Thickness of ten formulations from each batch was determined using Vernier calipers. The thickness variation limits allowed are ± 5% of the size of the formulation.

2.5.1.2. Weight Variation

Weight Variation study was carried out as per USP. Five formulations were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated.

2.5.1.3. Disintegration Test

Disintegration Test for the prepared formulation was carried out as per USP until it disintegrates using Disintegration tester (at 37±0.5^0 C) and 60rpm speed using 6.8 pH buffer for 20 mins.

2.5.1.4. Drug Content Determination

Drug content of a medicated chocolate was determined by using UV Spectrometer at 260nm against blank.

2.5.1.5. In Vitro Drug Release Studies

2.5.1.5.1. Dissolution conditions

Apparatus: USP II apparatus

Dissolution medium: 500ml of pH 6.8 Phosphate buffer

Temperature: 37±0.5^0 C

Rotating speed of the paddle: 50 rpm

Sample time intervals : 5, 10,15,20,25,30,35,40,45,50,55,60 minutes

Detection: UV-VIS spectrophotometer at λ_{max} 260 nm

Five ml aliquot samples were withdrawn at 5 min interval and replaced immediately with an equal volume of fresh medium i.e., phosphate buffer pH 6.8. Each aliquot samples were diluted appropriately and were analyzed spectrophotometrically at 260 nm. The cumulative percentage release and standard deviation were calculated.

3. RESULTS AND DISCUSSION

3.1. Evaluation Tests

3.1.1. Evaluation of Chocolate Base

3.1.1.1. Taste, Texture and Mouth Feel Characteristics Assessment

Taste, Texture & Mouth Feel Characteristics of chocolate base was determined by using 10 Human Volunteers & it was found to be satisfactory. It was scaled 1-5 under following characters which are shown in the table 5.

3.2. Evaluation of Medicated Chocolate

3.2.1. Evaluation of Physico-Chemical Properties

3.2.2. Drug Excipient Compatibility Studies

3.2.2.1. Differential Scanning Calorimetry

The DSC spectra of Chlorpheniramine Maleate showed sharp endothermic peak at 103^o C. DSC spectra of Medicated chocolate showed blunt endothermic peak at 104 ^{o} C. which shows that, the drug is in stable form in the chocolate formulation and there are no drug-excipient interactions. The DSC spectra are shown in the figures 1 and 2.

3.2.2.2. Fourier Transform Infra red Spectroscopy

FTIR spectra of pure drug Chlorpheniramine Maleate showed bands at 1580 cm^{-1} due to C=C stretching, 1476 cm^{-1} due to C-H stretching and 1352 cm^{-1} due to C-H bending, 864 cm^{-1} due to C-C and 702 cm^{-1} due to and C-Cl stretching vibration. The FTIR spectral bands are shown in the figures 3 and 4.

3.2.3. General appearance

Prepared formulations appear glossy and shiny. Prepared formulations are semi curvature in shape with length, width and height of 28.5, 18 and 14mm respectively as shown in the table 6.

3.2.4. Thickness

The thickness of the formulations was measured by using Vernier calipers. The mean thickness was almost uniform in all the batches and the values were found in the range of 8.99±0.02mm-9.18±0.05mm as shown in the table 7.

3.2.5. Weight Variation

The Weight Variation study was performed according to USP as shown in the table 8. The average percentage deviations of all formulations were in the range of 3.06±0.24gms-3.10±0.28gms respectively. The weights of all the formulations were almost uniform with low standard deviation values indicating effective mixing of the drug and excipients. The formulations showed no sign of sticking during preparation. Hence the formulations have passed the Weight Variation test.

3.2.6. Disintegration Test

Disintegration Test for the prepared formulation was carried out as per USP shown in the table 9. The average time taken for disintegration of formulations was almost uniform and they were in the range of 20±2mins-23±4mins respectively.

3.27. Drug content

For Chlorpheniramine Maleate medicated chocolate square drug content was found to be 98.49±0.54mg. The results are shown in the table 10.

3.2.8. In Vitro Drug Release (Dissolution)

Chocolate formulation was subjected to in vitro drug release using 6.8 PH Buffer.

Dissolution data shows that the first formulation releases complete drug within 60min. In time period of 5min, the drug release was found to be 25.10%, in 10min it was found to be 39.62%, in 15mins it was found to be 51.66%, in 20mins it was 75.06%, in 30mins it was 89.05%, in 45mins it was 99.00% and at last in 60mins it was found to be 100.00%. Dissolution data shows that the second formulation releases complete drug within 45min. In time period of 5min, the drug release was found to be 30.09%, in 10min it was found to be 42.62%, in 15mins it was found to be 66.88%, in 20mins it was 79.09%, in 30mins it was 98.05%, and at last in in 45mins it was 100.99% and there is no drug release remained for release in 60mins. Dissolution data of the third formulation shows that, it releases complete drug within 45min. In time period of 5min, the drug release was found to be 35.15%, in 10min it was found to be 45.62%, in 15mins it was found to be 67.85%, in 20mins it was 84.66%, in 30mins it was 99.05%, and at last in 45mins it was 101.62% and there is no drug release remained for release in 60 mins. The dissolution data of all the formulations are shown in the table 11. The percentage cumulative drug release profile of Chlorpheniramine Maleate in all formulations is shown in the figure 5.

4. CONCLUSION

It is concluded that, the Chlorpheniramine Maleate medicated chocolate formulations showed good drug release with 100% at 60min of F1, with 100.99% at 45 min of F2 and 101.62% at 45 min of F3 respectively were observed. Drug excipient compatibility studies reveals that, the drug is stable and showed no drug-excipient interactions. Since, artificial sweetening agents are used; it can also be used by diabetic patients.

5. REFERENCES

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Table 1: Formulation-I.

S. No	Ingredient	Category	Quantity
1.	Chlorpheniramine Maleate	Drug	4mg
2.	Cocoa powder	Principle ingredient	1446mg
3.	Cocoa butter	Solidifying agent	500mg
4.	Lecithin	Emulsifier	50mg

Table 2: Formulation-II.

S. No	Ingredient	Category	Quantity
1.	Chlorpheniramine Maleate.	Drug	4mg
2.	Cocoa powder	Principle ingredient	1350mg
3.	Cocoa butter	Solidifying agent	586mg
4.	Lecithin.	Emulsifier	45mg
5.	Pharmaceutical grade sugar	Sweetening agent	1000mg
6.	Pine apple flavour	Flavour	15mg
7.	Total	_	3000mg

Table 3: Formulation- III.

S. No	Ingredient	Category	Quantity
	Chlorpheniramine Maleate.	Drug	4mg

	Cocoa powder	Principle ingredient	1251mg
	Cocoa butter	Solidifying agent	500mg
	Lecithin.	Emulsifier	30mg
	Pharmaceutical grade sugar	Sweetening agent	1000mg
6	Mango flavour	Flavour	15mg
7	Dicalcium phosphate.	Adsorbent	200mg
8	Total	_	3000mg

Table 4:- Preparation of Chocolate Base.

S. No	Ingredient	Category	Quantity
	Cocoa powder	Principle ingredient.	1430mg
	Cocoa butter	Solidifying agent.	500mg
	Lecithin	Emulsifier.	50mg
	Pharmaceutical grade sugar	Sweetening agent.	1000mg

Table 5: Taste, Texture And Mouth Feel Characteristics Assessment.

S.NO	Character	Criteria	Scale
1.	Appearance	Glossy, even shine, no dots.	1-5 with 5 being the best.
2.	Aroma or smell	Chocolaty with only a light scent of any flavorings', fresh with no chemical smell.	1-5 with 5 being the best.
3.	Snap	Break clean without crumbling or layering.	1-5 with 5 being the best.
4.	Taste	Chocolaty, flavors not over powder the chocolate taste. Good after taste.	1-5 with 5 being the best.
5.	Texture	Creamy and smooth, not waxy; promptly and evenly melts in mouth.	1-5 with 5 being the best.

Table 6: General Appearance.

S.NO	Characteristics	Result
1.	Color	Dark brown
2.	Odor	Pleasant
3.	Taste	Semisweet
4.	Texture	Smooth

Table 7:- Thickness of Medicated chocolate formulations.

Formulation	Thickness (Mm).
F1	8.99±0.02
F2	8.36±0.09
F3	9.18±0.05

Table 8:- Weight variation of medicated chocolate formulations.

Formulation	**Weight Variation (Gms).**
F1	3.06±0.24
F2	3.02±0.30
F3	3.10±0.28

Table 9:- Disintegration of medicated chocolate formulations.

FORMULATION	DISINTEGRATION (mins).
F1	20±2
F2	22±1
F3	23±4

Table 10:- Drug content of medicated chocolate formulations.

Formulation	Drug Content (%).
F1	94.83±0.71
F2	98.49±0.54
F3	95.51±0.33

Table 11:- In vitro drug release studies of medicated chocolate formulations.

Time (min)	F1	F2	F3
0	0	0	0
5	25.10	30.05	35.15
10	39.62	42.62	45.62
15	51.66	66.88	67.85
20	75.06	79.09	84.66
30	89.05	98.05	99.05
45	99.00	100.99	101.62
60	100.00	--	--

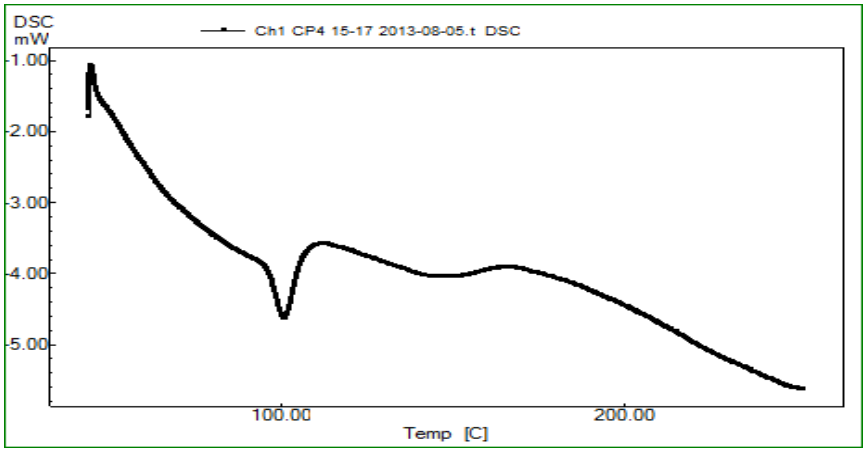

Fig. 1: DSC spectra of Chlorpheniramine Maleate.

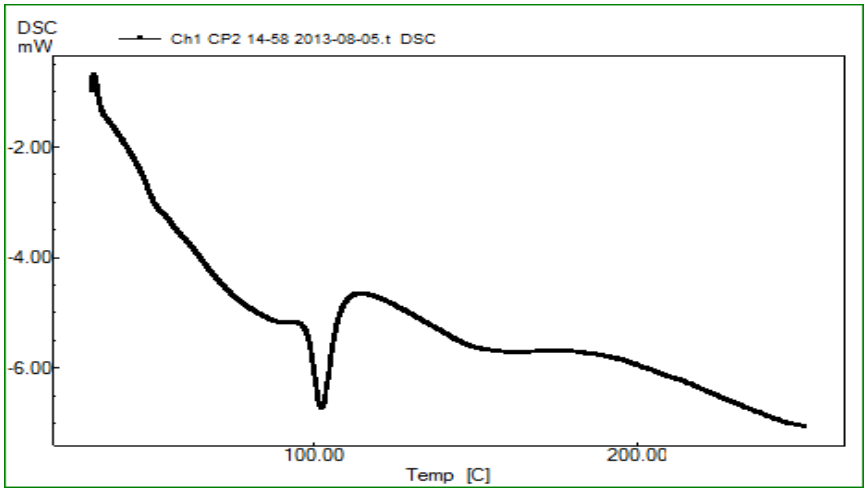

Fig. 2: DSC spectra of Medicated chocolate (Chlorpheniramine Maleate + Chocolate base).

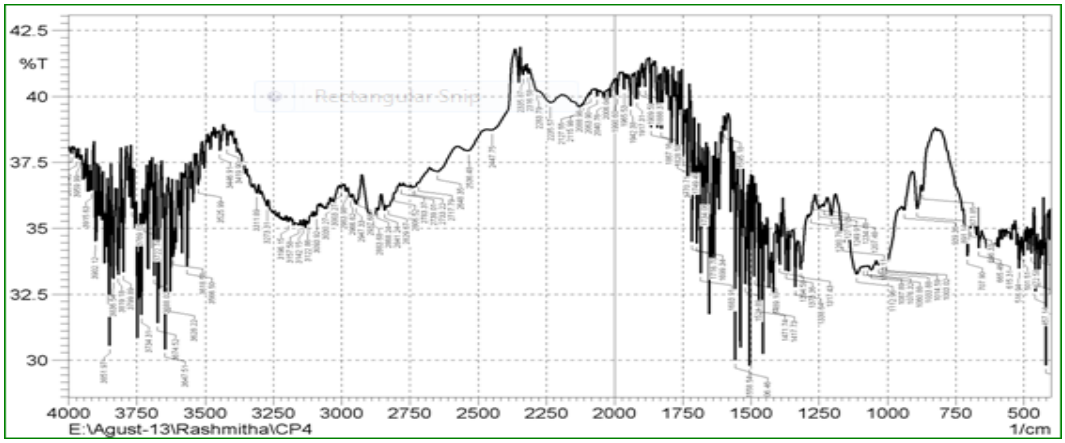

Fig. 3: FTIR spectra of Chlorpheniramine Maleate.

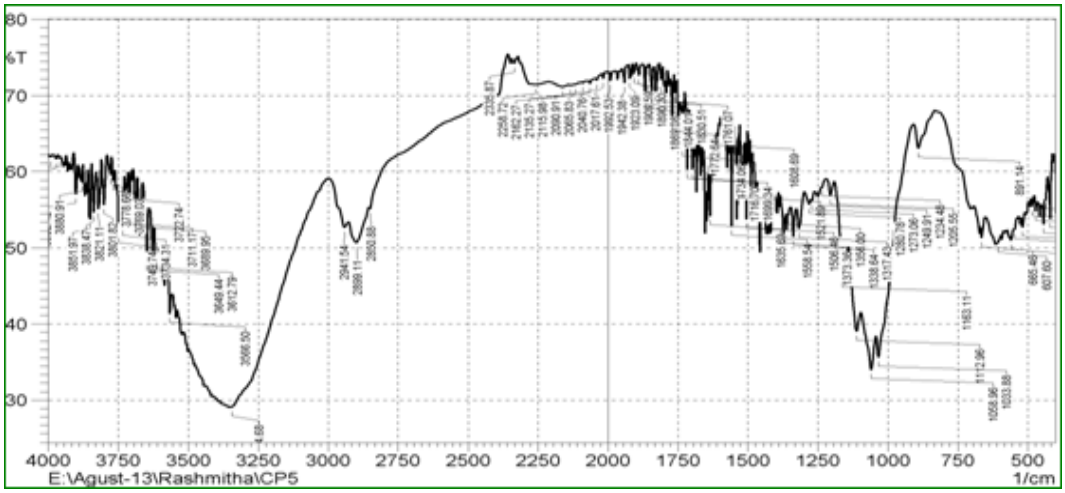

Fig. 4: FTIR spectra of Medicated Chocolate (Chlorpheniramine Maleate + Chocolate base).

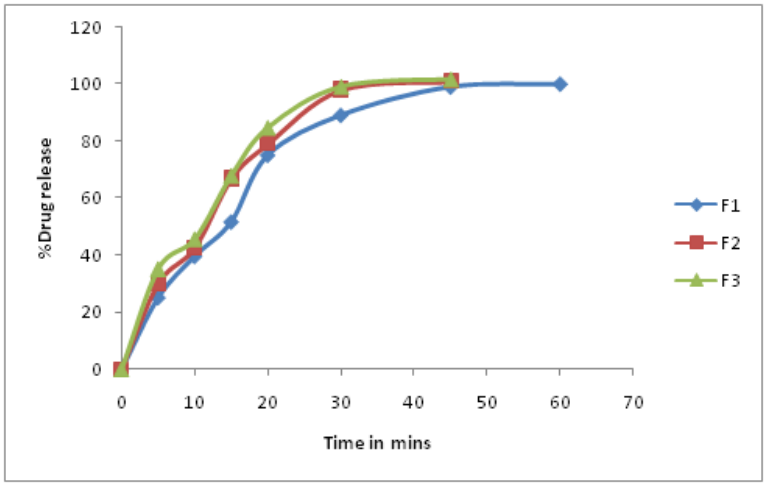

Fig. 5:- Percentage cumulative drug release profile of Chlorpheniramine Maleate.