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FORMULATION AND EVALUATION OF MEDICATED CHOCOLATE OF ATOMOXETINE

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Abstract: The purpose of this study to develop medicated chocolate of Atomoxetine. Atomoxetine is a prescription medicine used in the treatment of attention deficit hyperactivity disorder (ADHD). This medicine helps to modulates the activity of certain chemical messengers in the brain, which increases attention and decreases restlessness. The crucial aspect in formulation of medicated chocolate is to mask the bitter taste of drug. Initially the inclusion complex between Atomoxetine and beta cyclodextrin was prepared by kneading method. Different molar ratio of complex is prepared. Complex was characterized using FTIR spectroscopy, differential scanning calorimetry, % drug release study. Medicated chocolate containing Atomoxetine were prepared using ingredients like cocoa powder, cocoa butter, pharmaceutical sugar, lecithin, dicalcium phosphate, flavour. The initial compatibility studies between drug and excipients were carried out using DSC and FTIR spectra. The concentration of cocoa powder [X1] and cocoa butter [X2] were selected as independent variables. The hardness [Y1] and % CDR [Y2] were selected as dependent variables. The prepared medicated chocolate was evaluated for hardness, in vitro drug release, thickness, weight variation, drug content, moisture content, fat and sugar bloom. The results indicated that concentration of cocoa powder [X1] and cocoa powder [X2] were significantly affected the hardness [Y1] and %CDR [Y2]. Formulation F4 was found to be best formulation with % drug release in 30 min 9%. There was no drastic change in the results of medicated chocolate of an optimized batch at end of one month accelerated stability study.

KEYWORDS: ADHD, beta cyclo dextrin, Atomoxetine, DSC, FTIR

INTRODUCTION:

1.1 INTRODUCTION TO MEDICATED CHOCOLATE:

It is a complex and adaptable food that may be combined to create a wide range of taste and consistency sensations. Chocolate is an anhydrous medium for water-sensitive active agents that is resistant to microbial growth and hydrolysis. In many ways, chocolate is an excellent vehicle for delivering active agents. The organoleptic characteristics of chocolate, for example, are suitable for mask unpalatable flavors associated with some active agents and delivering a smooth and creamy texture to otherwise unappealingly abrasive active agent The organoleptic characteristics of chocolate, for example, are suitable for mask unpalatable

flavors associated with some active agents and delivering a smooth and creamy texture to otherwise unappealingly abrasive active agent formulations.

Saturated fat, polyphones, sterols, Di and triterpenes, aliphatic alcohols, and methylxanthines are all prevalent in chocolate. Chocolate's main constituent is cocoa, which is high in polyphones, especially flavan-3-ols like epicatechins, catechins, and procyanidins. A high intake of dietary flavonoids, a subgroup of polyphenols, may reduce the risk of coronary heart disease, according to research.

Antioxidants protect cells from free radical damage produced by biological functions like breathing and external impurities like cigarette smoke. Free radicals cause damage to our bodies when we don't eat enough antioxidants. Increased oxidation, for example, might cause plaque to form on the artery walls due to low-density lipoprotein (LDL), generally known as "bad" cholesterol.

Chocolate also has medical benefits, such as lowering blood pressure, changing blood flow to the brain, preventing cell damage, and improving glucose levels. It also reduces the risk of heart attack, improves HDL cholesterol, and lowering LDL cholesterol.

However, chocolate has multiple benefits such as a rapid initiation of action, ease of manufacture and scale, reduced drug dose, and increased drug loading capacity.[1]

Types of Chocolates:

Milk chocolate: It is recommended that you use mostly medium roast West African beans with Ecuadorian beans. This blend would produce a clean, nutty, slightly fruity chocolate. It's important to remember that the addition of the more acidic Brazilian and Malaysian beans should battle with the desired creamy flavors.

Light milk chocolate: This product could be prepared with slightly roasted java beans, which have a light color and a mildoverall flavors with strong nutty overtones.[2]

High-quality semisweet chocolate: To highlight ideal notes and reduce burnt/bitter notes, use mostly West African stock (light to medium roast) for its chocolate flavor and slightly nutty undertones. When mixed with Caracas and Trinidad beans, this blend produces a balanced yet unique profile with sweet and rather spicy overtones.

Bittersweet chocolate: this product is mainly designed for use on very sweet and highly flavored cream centers as it produces very bitter coatings.

Semisweet cookie drops: In order to have a good cocoa impact, it is recommended that the dominating West African beans be used in this product.[3]

1.2 INTRODUCTION TO ADHD: (ADHD) is a neurodevelopmental disorder characterized by excessive amounts of inattention, hyperactivity, and impulsivity that are pervasive, impairing in multiple contexts, and otherwise age-inappropriate.[4]

ADHD is associated with other neurodevelopmental and mental disorders as well as some non-psychiatric disorders, which can cause additional impairment, especially in modern society. Although people with ADHD struggle to focus on tasks they are not particularly interested in completing, they are often able to maintain an unusually prolonged and intense level of attention for tasks they do find interesting or rewarding; this is known as hyperfocus.[5]

ADHD management recommendations vary and usually involve some combination of medications, counseling, and lifestyle changes. The British guideline emphasizes environmental modifications and education for individuals and carriers about ADHD as the first response. If symptoms persist, parent-training, medication, or psychotherapy (especially cognitive behavioral therapy) can be recommended based on age. Canadian and American guidelines recommend medications and behavioral therapy together, except in preschool-aged children for whom the first-line treatment is behavioral therapy alone. Stimulant

medications are the most effective pharmaceutical treatment, although there may be side effects and any improvements will be reverted if medication is ceased.[6]

ADHD, its diagnosis, and its treatment have been considered controversial since the 1970s. These controversies have involved doctors, teachers, policymakers, parents, and the media. Topics have included causes of ADHD and the use of stimulant medications in its treatment. ADHD is now a well-validated clinical diagnosis in children and adults, and the debate in the scientific community mainly centers on how it is diagnosed and treated. ADHD was officially known as attention deficit disorder (ADD) from 1980 to 1987; prior to the 1980s, it was known as hyperkinetic reaction of childhood. Symptoms similar to those of ADHD have been described in medical literature dating back to the 18th century.[7]

ADHD is often comorbid with disruptive, impulse control, and conduct disorders. Oppositional defiant disorder (ODD) occurs in about 25% of children with an inattentive presentation and 50% of those with a combined presentation. It is characterized by angry or irritable mood, argumentative or defiant behavior and vindictiveness which are age-inappropriate. Conduct disorder (CD) occurs in about 25% of adolescents with ADHD. It is characterized by aggression, destruction of property, deceitfulness, theft and violations of rules. Adolescents with ADHD who also have CD are more likely to develop antisocial personality disorder in adulthood. Brain imaging supports that CD and ADHD are separate conditions, wherein conduct disorder was shown to reduce the size of one's temporal lobe and limbic system, and increase the size of one's orbitofrontal cortex, whereas ADHD was shown to reduce connections in the cerebellum and prefrontal cortex more broadly.[8]

2.1 List of Materials

SR NO	MATERIALS	NAME OF THE COMPANY
1.	Atomoxetine	Healing Pharma India Pvt ltd
2.	Cocoa powder	Yarrow Chemicals, Pvt ltd
3.	Cocoa butter	Yarrow Chemicals, Pvt ltd
4.	Lecithin	Himedia laboratories Pvt ltd
5.	Dicalcium phosphate	Himedia laboratories Pvt ltd
6. sugar	Pharmaceutical grade	Yash Pharma sugar
7.	Pineapple flavor	Nutra Healthcare Pvt ltd
8.	Beta - Cyclodextrin	R P Chemical

2.2 List of Equipments

Sr no	Equipment's	Manufactures
1.	Digital weighing balance	Shimadzu
2.	FTIR [Fourier Transform Infrared Spectroscopy]	Shimadzu, Japan
3.	UV Visible spectrophotometer	Analytical Technologies. Ltd
4.	Dissolution Apparatus	DS 8000 lab India instruments Pvt ltd
5.	Hardness tester	Presto Stantest Pvt. ltd
6.	Differential scanning calorimeter	Mettler Toledo
7.	Bath sonicator	Labman, scientific instrument
8.	Melting point apparatus	Guna instruments

3.1 METHODOLOGY:

3.1.1 PREFORMULATION STUDIES: Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting identification of new active agents to characterizing physical properties necessary for the design of dosage forms. Critical information provided during the preformulation can enhance the rapid and successful introduction of new therapeutic entities for humans. Hence preformulation studies are essential to characterization drugs for proper designing of drug delivery systems.

3.1.2 Determination of λ max of Atomoxetine in phosphate buffer pH 7.4: 10mg of drug was transferred into 10 ml volumetric flask and dissolved into 7.4 pH buffer solution. Flask was shaken and volume make up to mark with 7.4 pH buffer to get 1000 µg/ml solution. From this stock solution pippete out 1 ml and place into 100 ml volumetric flask volume was make up to mark with 7.4 pH buffer solution to get solution containing 10 µg/ml which was further diluted with same and scanned between wavelength of 200-400nm**.**

3.1.3 Calibration curve for atomoxetine: 50mg was dissolved in phosphate buffer pH 7.4 in 50 ml volumetric flask (SSI). From SSI, 10ml solution was transferred to 50 ml volumetric flask and volume was made up with phosphate buffer pH 7.4 (SSII). From SSII, 10 ml solution was transferred to 50 ml volumetric flask and volume was made up with phosphate buffer pH7.4 (SSIII). 1, 2, 3, 4 and 5ml from SSIII were transferred to 10 ml volumetric flasks and diluted up to the mark to give 5, 10, 15, 20 and 25 µg/ml solutions respectively. The absorbance of these solutions was determined in a UV spectrophotometer at 274 nm and calibration curve was plotted.[9]

3.1.4 Drug excipients interaction study

	INGREDIENTS	FUNCTIONS
1.	Atomoxetine	API
2.	Cocoa butter	Lubricant
3.	Cocoa powder	Flavoring agent

To study the compatibility of various formulation excipients with Atomoxetine, solid mixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and it was filled enclosed vial sand placed instability chamber at 30±2 °C/65±5%RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR) The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT- IR).[10]

3.1.5 Taste Masking of Atomoxetine using: β-Cyclodextrin : In order to achieve more pleasant dosage forms various taste masking techniques have been described. simplest method is to add flavor or sweetener. In most cases is not enough to mask unpleasant taste of some drugs. Development of medicated chocolate is challenging is due to its bitter taste for taste masking of atomoxetine inclusion complex technique was employed using beta cyclodextrin.[11]

3.1.6 Method of preparation of taste masked inclusion complex of Atomoxetine with β-cyclodextrin by kneading method:

Amount of atomoxetine and beta cyclodextrin to give 1:0.5, 1:1, 1:2 molar ratios were weighed thoroughly mixed then triturated by addition of few drops of methanol in mortal pestle. the slurries were kneaded for 60 mins to get paste and dries for 40 degrees Celsius the dries complex was sieved through 80# and stored in airtight container.

3.1.7 Fourier Transform Infrared Spectroscopic Analysis: Atomoxetine, beta cyclodextrin and inclusion complex were subjected for FTIR studies samples were prepared using KBr disc method and spectra was recorded. spectra were analyzed for drug – beta cyclo dextrin interaction and functional group involved in complexation process

3.1.8 Differential Scanning Calorimetry (DSC) Analysis: DSC scan of powdered samples of drug, beta cyclo dextrin and kneaded complex were recorded using DSC instrument. The thermal traces were obtained by heating complex from 40 to 350 degree Celsius at heating rate of 10 degree Celsius under inert nitrogen dynamic atmosphere (100ml/min) in open aluminum crucibles.[12]

3.1.9 Method of preparation: The oven temperature was set at 50 °C. The chocolate foundation was then heated until it was a free-flowing liquid. Following the preceding procedure, the needed amount of medication was added. The whole material was then thoroughly agitated with the assistance to guarantee equal mixing, use a magnetic stirrer. The liquid was then put into a polycarbonate set mold and chilled for 15 minutes until firm. The five formulations of medicated chocolates were created. A batch of ten units of the I formulation was made, with each unit containing Atomoxetine medication, Cocoa Powder, Cocoa Butter, Lecithin, and Pharmaceutical Grade Sugar blended equally and in the right sequence to create a medicated chocolate formulation. But there was an issue with the sense of odor. The cocoa powder odor was highly dominant and powerful to smell when producing the formulation, and a pungent fragrance created by lecithin was also detected while testing the formulation. As a result, a taste was added to mask the strong and pungent aromas of cocoa powder and lecithin.In order to create a medicated chocolate formulation, a batch of ten units containing Atomoxetine medication, Chocolate Powder, Cocoa Butter, Lecithin, Pharmaceutical Grade Sugar, and Pine apple taste were blended uniformly and in the appropriate sequence. Moreover, taste was added to this formulation in order to disguise the strong odour and pungent scent of cocoa powder and lecitthin As a result of correct solidification of the formulation when collecting the prepared medicated chocolate from the molds, there is a risk of formulation breakage and, as a result, poor shape of the formulation. To address this issue, an adsorbent Dicalcium phosphate was added to the formulation.

In order to create a medicated chocolate formulation, a batch of 10 formulations including Atomoxetine medication, Cocoa Powder, Cocoa Butter, Lecithin, Pharmaceutical Grade Sugar, Mango taste, and Dicalcium Phosphate were blended uniformly in the appropriate sequence.

Moreover, Dicalcium Phosphate was added to the formulation to aid in the correct solidification of the formulation when removing the prepared medicated chocolate from the molds. The type of taste utilized has changed, with Mango flavor in formulation III replacing Pine apple flavor in formulation II. When compared to Mango flavor, the formulation with Pine Apple flavor was far more palatable. In terms of odor and taste, Pine apple flavor approval is extremely high. Similarly, batches of formulation IV and V also prepared.[13-15]

INGREDIENTS	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
ATOMOXETINE + BETA CYCLO DEXTRIN [1:0.5]	55mg	55mg	55mg	55mg	55mg	55mg	55mg	55mg	55mg
COCOA POWDER	1446mg	1446mg	1446mg	1350mg	1350mg	1350mg	1250mg	1250mg	1250mg
COCOA BUTTER	560mg	530mg	500mg	560mg	530mg	500mg	560mg	530mg	500mg
LECITHIN	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg
PHARMACEUTICAL SUGAR GRADE	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg
PINEAPPLE FLAVOUR	2 drops	2 drops	2 drops	2 drops	2 drops	2 drops	2 drops	2 drops	2 drops
DICALCIUM PHOSPHATE	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

3.1.10 EVALUATION PARAMETERS OF MEDICATED CHOCOLATE

3.1.10.1.Physical Observation:[16]

Ten medicated chocolate was weighed and observed physically to study the surface characteristics and shape. Surface characteristics and shape of the medicated chocolate was evaluated by physical observation. It is important to check for the absence of pitting, fat blooming, sedimentation and migration of active ingredients

3.1.10.2. Weight Variation:[17]

Medicated chocolate can be weighed on an automatic balance, obtaining the weight of medicated chocolate. All the medicated chocolate was weighed and average weight was calculated. Then all the medicated chocolate was weighed individually and the variation from average weight was calculated.

3.1.10.3. Thickness and diameter:[18]

The thickness and diameter of the ten medicated chocolate is the only dimensional variable related to the molding process. Thickness and diameter of the dosage form were measured by Vernier caliper. The deviation of each is calculated and the deviation of individual unit from the mean diameter should not exceed ± 5%

3.1.10.4 .Determination of Drug Content:

Drug content of a medicated chocolate was measured by dissolving it in 10 ml ethanol and it is sonicated. Then this sonicated mixture was centrifuged for 15 min at 2500 rpm. Supernatant solution was filtered to remove any chocolate traces and the drug content was analyzed and determined by using UV Spectrometer at 274 nm for atomoxetine.

3.1.10.5. Determination of Moisture content:[19]

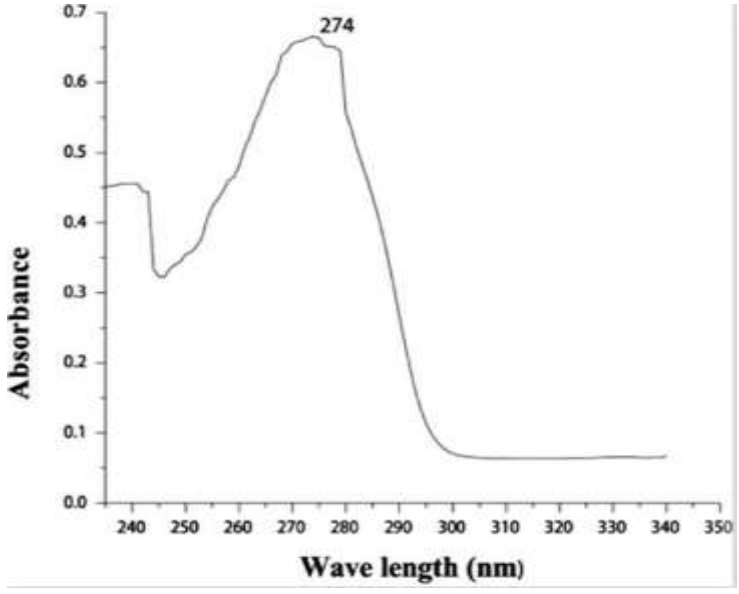
Moisture content of medicated chocolate was determined by keeping it inside the desiccator under reduced pressure by applying vacuum for 24 hours. Initial weight and the final weight after 24 hrs.

3.1.10.6 IN VITRO DRUG RELEASE

In vitro drug release study of medicated chocolate was performed in USP dissolution apparatus Type II (Rotating Paddle), using pH 7.4phosphate buffer as a dissolution media. The bowls of the dissolution tester was filled with 900mL of pH 7.4 phosphate buffer was placed and allowed to attain a temperature of 37±0.5ºC and 50rpm. A chocolate formulation was placed in the basket. At predetermined time interval i.e., 1, 2, 3, up to 60 minutes, 10mL sample was withdrawn and volume was replaced with equal quantity of fresh medium. The collected samples were filtered and analyzed by UV Spectroscopy at 274nm for Atomoxetine.[20][21]

3.1.10.6 stability studies: Since the period of stability testing can be as long as two years, it is time consuming and expensive. Therefore, it is essential to devise a method that will help rapid prediction of long- he term stability of drug. The stability may be predicted defined as the validated method by which the product stability may be predicted by storage of the product under conditions that accelerate the change in defined and predictable manner. The stability studies of formulated formulations were carried out at 25 ºC / 75 % RH and 2-8 ºC for one month. The effects of temperature, humidity and time on the general appearance of chocolate and drug content were evaluated for assessing the stability of the prepared formulation.[22][23]

RESULT AND DISCUSSION:



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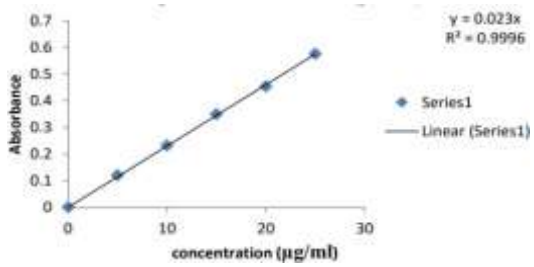
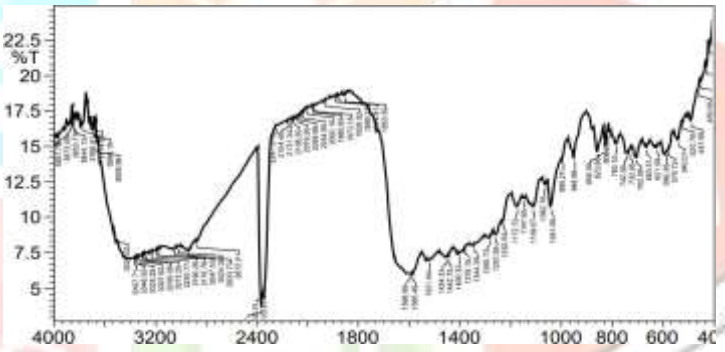


3.1.3

Concentration(µg/ml)	Absorbance
5	0.12
10	0.23
15	0.34
20	0.45
25	0.57

3.1.4

(A)



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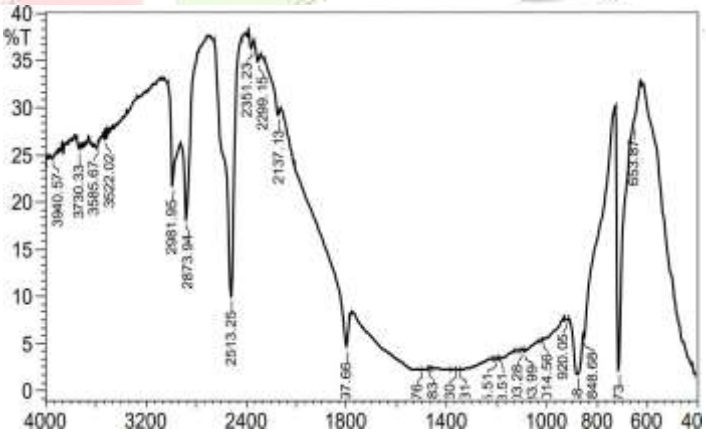

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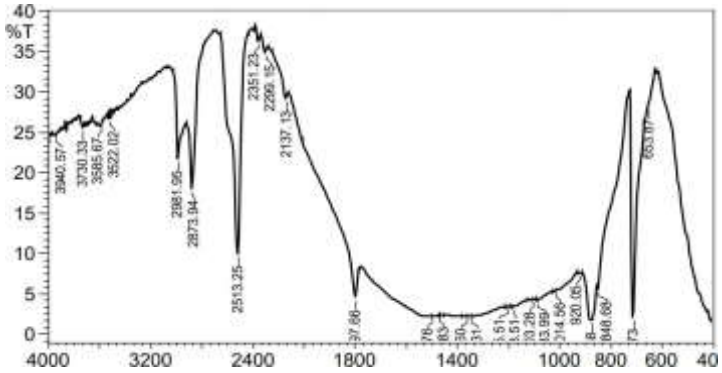
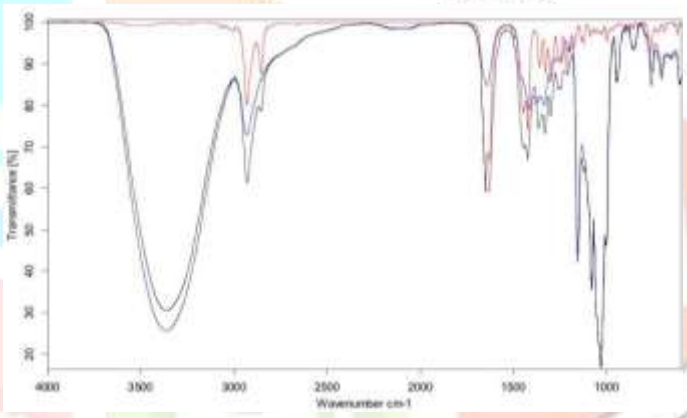


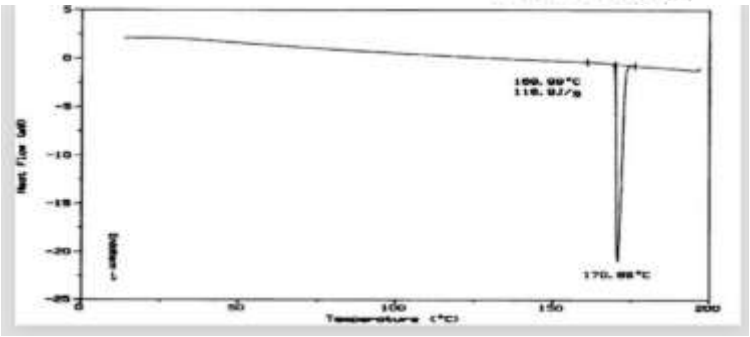
Compatibility studies of pure drug atomoxetine were carried out prior to the formulation of medicated chocolate. IR spectra of pure drug and excipients were taken. All the characteristic peaks of atomoxetine were present in spectra at respective wavelengths. Thus, indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug. Compatibility study is important to understand the interaction between the drug and excipients. It saves costs and it makes easier to choose a few excipients from the long list of excipients for a better formula

(d)



FTIR spectra of prepared complexes, atomoxetine bands are almost completely obscured by very intense and broad CD bands are hardly influenced by complex formulation

(a)



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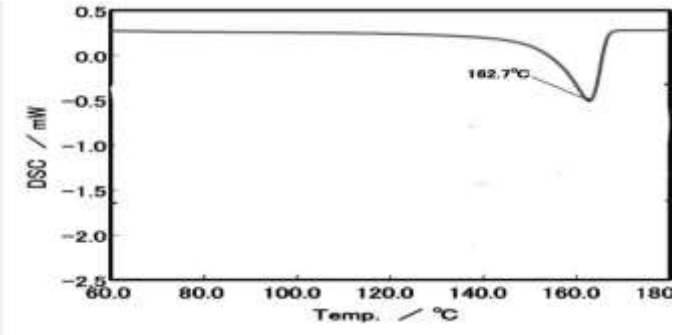

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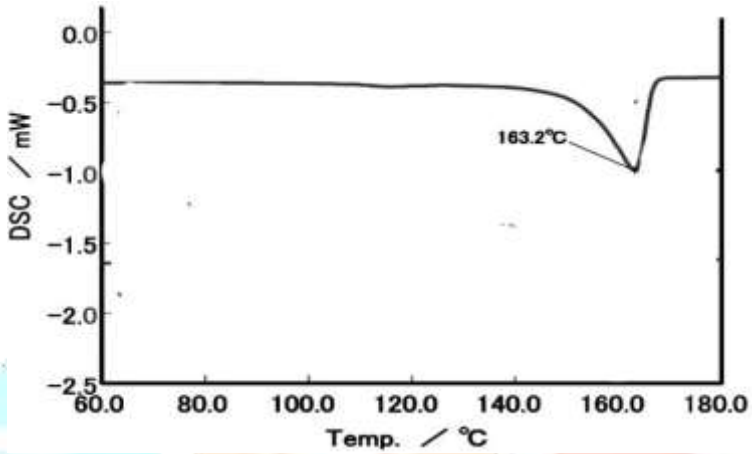
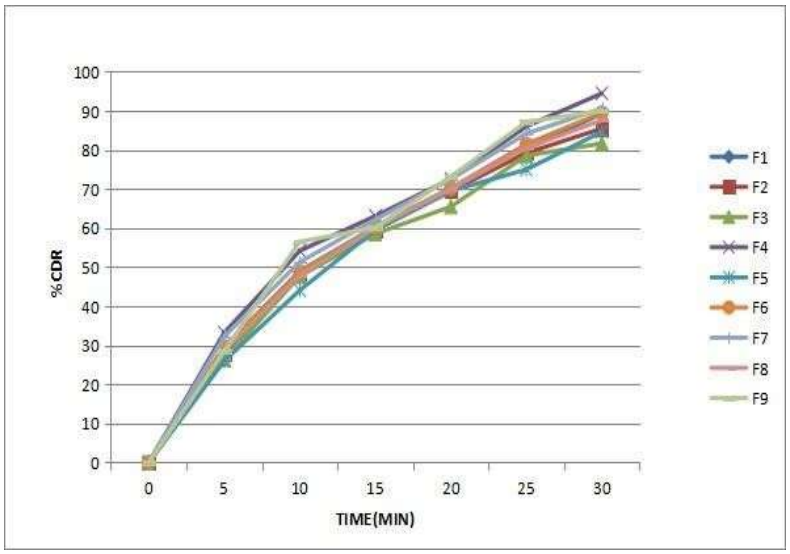


DSC OF atomoxetine, beta cyclo dextrin, inclusion complex (1:1) molar ratio is there. Atomoxetine has sharp peak at 171 degrees Celsius. the existence interaction between two components can be obtained by DSC. When guest molecules are included in beta cyclo dextrin cavity, their melting, boiling, and sublimation point usually shift to different temperature. on the other hand, no intense peak over melting range of atomoxetine was found in DSC thermogram of inclusion complex which clearly indicates that drug was completely embedded in beta cyclo dextrin cavity and confirmation of complexation.

3.1.6 EVALUATION

FORMULATION	WEIGHT	THICKNESS	DRUG CONTENT	MOISTURE CONTENT	HARDNESS	SUGAR AND FAT BLOOM
F1	3.12	8.21	78.3%	1.23	3.16	NO
F2	3.20	8.16	79%	1.44	3.14	NO
F3	3.16	8.49	87%	1.23	3.22	NO
F4	3.36	9.11	91%	1.65	3.34	NO
F5	3.25	8.65	89%	1.50	3.16	NO
F6	3.30	8.74	87%	1.49	3.18	NO
F7	3.11	8.66	88%	1.42	3.11	NO
F8	3.14	8.44	79%	1.38	3.05	NO
F9	3.11	8.32	70%	1.22	3.01	NO



TIME IN MINS	F1	F2	F3	**F4**	F5	F6	F7	F8	F9
0	0	0	0	**0**	0	0	0	0	0
5	29.56	28.05	26.36	**33.25**	26.01	29.55	32.26	28.55	28.60
10	49.01	48.50	47.69	**54.20**	44.10	48.90	51.33	47.90	56.50
15	60.25	59.56	58.55	**63.09**	59.50	60.25	62.20	60.10	60.15
20	70.20	69.50	65.49	**72.56**	69.52	70.21	72.50	70.01	70.15
25	80.23	79.22	78.55	**86.05**	75.01	81.50	84.20	80.50	80.59
30	89.36	85.51	81.69	**94.50**	84.65	89.54	90.63	87.63	87.78

3.1.9 STABILITY STUDY

OBSERVATION	**7 days**	**15 days**	**30 days**
Color	Dark brown	Dark brown	**Dark brown**
Odor	Pleasant	Pleasant	**Pleasant**
Appearance	Glossy	Glossy	**Glossy**
Fat bloom	Absence	Absence	**Absence**
Sugar bloom	**Absence**	**Absence**	**Absence**

3.10 Conclusion:

This study aims in formulating an effective and attractive dosage form in pediatrics. Atomoxetine used as key ingredient in medicated chocolate formulation. Atomoxetine beta cyclo dextrin inclusion complex formulation mask the bitterness which helps pediatric patient for the treatment of ADHD. Invitro results shows significant drug release revealed that F4 is optimized formulation are kept for stability study. Overall, this study reports concluded that the formulated Medicated chocolate offers an effective oral dosage form when compared with existing formulations, leading to an attractive dosage form for pediatrics with better patient compliance.

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