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FORMULATION AND IN – VITRO CHARACTERIZATION OF MEDICATED CHOCOLATES FOR PEDIATRICS

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ABSTRACT

Chocolate is highly sophisticated and infinitely a versatile food that can be combined to create completely different taste and sensations. The objective of the present research work is to develop a palatable chocolate formulation of Montelukast for paediatric administration and to increase patient compliance. In present investigation the medicated chocolates were prepared by two methods using cocoa powder, cocoa butter, lecithin, powdered sugar and using compound chocolate base. Lecithin used during formulation increased the hardness of chocolate.The prepared medicated chocolate were characterized for physical characteristics, drug content and in vitro drug release. Study indicated that both the methods used in the formulation had similar drug release pattern. Batch F4 showed 95.07% at 30 mins whereas F5 showed 93.55% at 30 mins. The formulated chocolate was slightly bitter in taste but is a convenient form of dosage form for paediatrics.

KEYWORDS: Medicated Chocolate, Paediatric, Montelukast, Lecithin.

INTRODUCTION

Paediatric formulations can be quite scientifically challenging to develop due to unique requirements and limitations. A Different challenges for developing paediatric formulation includes diversity of children, taste masking, stability – physical, chemical, microbial, achieving global regulatory acceptability, providing rapid patient access and accelerated development studies. (JankiPatel et al, 2016).Chocolate is highly sophisticated a versatile food that is combined to create completely different taste and texture sensations. 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. For example, the organoleptic characteristics of chocolate are excellent for masking unpleasant flavours associated with some active agents and giving a smooth and creamy texture to compositions of active agents that are otherwise undesirably gritty (JankiPatel et al,2016).Chocolate abundantly contains compounds such as saturated fat, polyphenols, sterols, di and tri terpenes, aliphatic alcohols, and methyl xanthine. 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.(JankiPatel et al,2016).

Cocoa is the principle ingredient of chocolate and it is rich in polyphenols, particularly in flavan-3-ols such as epicatechins, catechins, and procyanidins. Research studies suggest that a high intake of dietary flavonoids, a subgroup of polyphenols, may reduce the risk of coronary heart disease. (Sharma Mayank et al, 2012).Cocoa containing flavonoids have antioxidant property. 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.(Sharma Mayank et al, 2012).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.

Taste is defined as “the sensation of flavor perceived in the mouth on contact with a substance”. A food or medication that is palatable is one that is “pleasant to taste” (Oxford Dictionary, 2007). The primary cells for taste are modified epithelial cells that are grouped in taste buds and are found in the taste papillae of the tongue (Llorens et al.,2004).There are four basic taste modalities, sweet, salty, sour and bitter. Children’s tastes sensation is differ from adults (Mennella et al.,2005). Infants and children have a preference for sweet-tasting substances (Lawless et al.,1985)that decreases to resemble that of adults during late adolescence (Liem et

al.,2002)**.**On the other hand, aversion to bitterness appears from a very early age and, therefore, bitter flavors are likely to decrease palatability. Indeed, addition of aversive bittering agents has been proposed as a method of preventing toxic ingestions in young children(Rodgers et al.,1994).

Medicated chocolate is prepared by using chocolate base and the drug is incorporated into prepared chocolate base. As the drug is incorporated within the chocolate and the drug is released from the chocolate, it is called as Chocolate drug delivery system.

Soy lecithin is a phospholipid derived from soybeans. Practically, it's an industrial waste product it is extracted from the sludge that is left after the soy oil undergoes a degumming process. This is why soy lecithin is the most common type of lecithin on the market; it is a by product which is easily andinexpensively derived fromsoybean oil manufacturing. Physically, it presents itself in liquid form as a yellow-brownish fatty substance with a fairly thick viscosity.The polymorphic nature of the cocoa butter requires the tempering of the chocolate melt during the production process, in order to obtain the most adequate crystal form, denominated as β Form.Emulsifiers are used in chocolate formulations as rheological properties improvers.Commercial soy lecithin containing 62 to 70% of phospholipids are added in order to depress the plastic viscosity of the mass.

Lecithin has a negligible effect on yield stress if used at a concentration between 0.1 and 0.3%. Between 0.3 and 0.5%. The best time to add soy lecithin to the chocolate is at the last stage, since it takes only a few minutes for lecithin to incorporate.

Chocolate drug delivery system has advantages

- A possible bypass of first-pass effects
- Avoidance of pre-systemic 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.

Montelukast, like zafirlukast, is a leukotriene receptor antagonist used as an alternative to anti-inflammatory medications in the management and chronic treatment of asthma and exercise-induced bronchospasm (EIB). Unlike zafirlukast, montelukast does not inhibit CYP2C9 or CYP3A4 and is, therefore, not expected to affect the hepatic clearance of drugs metabolized by these enzymes. Montelukast selectively antagonizes leukotriene D4 (LTD4) at the cysteinyl leukotriene receptor, CysLT1, in the human airway. Montelukast inhibits the actions of LTD4 at the CysLT1 receptor, preventing airway edema, smooth muscle contraction, and enhanced secretion of thick, viscous mucus.

Rapidly absorbed following oral administration (bioavailability is 64%).Volume of distribution is 8 to 11 L and plasma protein binding is 99%.

Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.The Half life is 2.7-5.5hours, Clearance rate is 45 mL/min [healthy adults]. Side effects include headache, abdominal or stomach pain, cough, dental pain, dizziness, fever, heartburn, skin rash, stuffy nose, weakness or unusual tiredness. Mostly affected organisms are humans and other mammals.

EXPERIMENTAL WORK

Method of Preparation of Medicated chocolate

The medicated chocolate was prepared by two subsequent methods.

A. Preparation using compound chocolate

Required amount of compound chocolate was weighed and melted in china dish using electric water bath, then required amount of drug was weighed and added to the melted chocolate. This mixture was then poured to the silicon mould and kept for refrigeration.

B. Preparation using cocoa powder

Ingredients for chocolate base were weighed and sieved (sieve no: 30). In the mixture of ingredients was added to melted cocoa butter and lecithin. With the help of glass rod the mixture was stirred for about 15-20mins for getting pourable consistency.Required amount of drug was weighed and added to the chocolate base and this mixture was poured to the silicon mould and kept for refrigeration. But a problem occurred when the chocolates were formed, the chocolates got melted within 5-10 mins at room temperature.

Drug characterization

A. Organoleptic Properties

The colour, odour, taste, and physical appearance of drug were observed visually.

B. Melting Point

Melting point of montelukast was determined by using open capillary tube method. Pure drug was filled in a capillary tube which was sealed at one end and placed in a digital melting point apparatus. The temperature noted where melting was start.

C. Solubility Studies

A solubility study was carried out to find out the solubility of drug in different solvents. According to this method, the pure drug was added to the solvent medium and shaken for 2 hr. The saturation was confirmed by observation of presence of un-dissolved material.

D. UV-Visible Spectrophotometric Analysis

Standard calibration curve of montelukast in methanol:- Standard stock solution of montelukast prepared by

dissolving 10 mg of drug in 10 ml of methanol in 10ml volumetric flask, final volume was adjusted with methanol and sonicated for 10 min to get 1000μg/ml working standard. Solution of 100μg/ml was scanned in the entire UV range of 200-400 nm to obtain the absorbance.Working stock solution of five different concentrations was prepared with different concentration of ranges 2, 4, 6, 8 & 10μg/ml in methanol and absorbance were analysed at the λmax.

Evaluation of prepared medicated chocolate

A. Texture and consistency:(JankiPatel et al,2016).
Medicated chocolate in terms of stickiness and grittiness was evaluated by visual inspection of the product after mildly rubbing the chocolate sample between two fingers.

B. Weight variation: (Reddy sunil et al, 2017)
Weight Variation study was carried out as per USP. Ten formulations were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated.

C. Thickness: (Reddy sunil et al, 2017)
The 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.

D. Hardness:(JankiPatel et al,2016)
Chocolate crushing strength, which was the force required to break the chocolate, was measured with a monsanto tablet hardness tester. The hardness (crushing strength) of three medicated chocolate per batch was determined and mean were taken.

E. Disintegration test: (Reddy sunil et al, 2017)
Disintegration Test for the prepared formulation was carried out as per USP until it disintegrates using Disintegration tester(at 37±0.5 °C) and 60rpm speed using distilled water.

F. Determination of drug content in the medicated Chocolate:(JankiPatel et al,2016).
Drug content of a medicated chocolate was determined by using UV Spectrometer. Medicated chocolate was taken in 25 ml beaker and dissolved in 10 ml of methanol & sonicated. Then this sonicated mixture was poured in a centrifuge tubes. It was then centrifuged for 15 min at 2500 rpm. Upper layer having clear liquid containing dissolved drug and solid part of chocolate base was settle down on bottom. This supernatant was then filtered to remove any traces of chocolate remaining in it. Then this liquid sample was analysed using by UV spectrophotometer against methanol as a blank.

G. In-vitro Drug release studies
In vitro drug release was studied using USP II apparatus,with 500 ml of dissolutionmedium maintained at 37±1°C for 1h (5,10,15,20,25,30,35,40,45,50,55, 60min), at 50 rpm. pH 6.8 Phosphate buffer was used as a dissolution medium. 5 ml of sample was withdrawn in different time intervals and was replaced by an equal volume of fresh dissolution medium of the same pH. Collected samples were analyzed spectrophotometrically at 286 nm, and cumulative percent drug releasewas calculated.

RESULTS AND DISCUSSION

Drug characterization

A. Organoleptic properties
The colour, odour, taste, and physical appearance of drug were observed visually.

Table No. 1: Organoleptic Properties of Drug.

Sr.no	Parameters	Observation
1	Colour	Whitish yellow
2	Odour	Odourless
3	Taste	Bitter
4	Nature of powder	Amorphous powder

B. Melting point
The melting point of the drug sample was found in the range of 140^0c to 145^0c. From this observation it was near to the actual range of drug which is reported.

Table No. 2: Melting Point of montelukast.

MELTING POINT	OBSERVATION
140°c to 145°c	140°c to 145^0c

C. Solubility studies
Solubility of drug in various solvents observed visually. From the observations it seems that drug was soluble in methanol and insoluble in water and buffer.

Table No. 3: Solubility Studies.

Sr. no.	Solvent	Solubility
1	Water	Insoluble
2	Methanol	Soluble
3	Buffer	Insoluble

D. Uv-visible spectrophotometric analysis
Standard calibration curve of montelukast in methanol.

Table No. 4: Absorbance of montelukast.

Sr. No.	Concentration(µg/ml)	Absorbance
1	2	0.0934
2	4	0.245
3	6	0.45
4	8	0.6
5	10	0.809

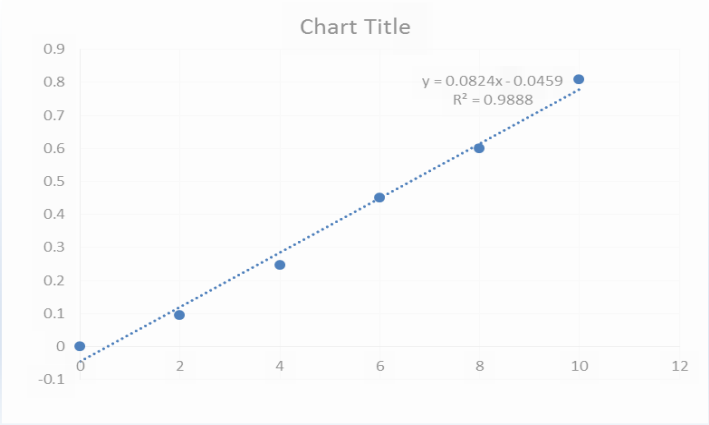

Fig No.1: Calibration curve of montelukast in methanol.

Formulation characterization

Table No. 6.1: Composition of Medicated chocolate.

Sr. no	Ingredients	F1	F2	F3	F4	F5
1	Montelukast	80mg	80mg	80mg	80mg	80mg
2	Cocoa powder	84mg	84mg	84mg	84mg	-
3	Cocoa Butter	2g	2g	2g	2g	-
4	Powdered sugar	1g	1g	1g	1g	-
5	Lecithin	-	0.3%	0.4%	0.5%	-
6	Compound chocolate	-	-	-	-	3g

(a)Formulation of chocolate without lecithin.

(b)Formulation of chocolate with lecithin (0.3%)

(c) Formulation of chocolate with lecithin (0.5%).

(d) Formulation of chocolate with lecithin (0.4%).

(e) Formulation of chocolate using compound chocolate.

A. General Appearance

The prepared chocolates were evaluated for general appearance, colour and taste and results were reported in table no. 5. All the chocolates were found to be brown in colour with no streaks and even shine and were slightly bitter.

Table No. 5: General appearance of Medicated chocolate.

Formulation code	Appearance	Colour	Taste
F1	Slightly glossy, few streaks	Brown	Slightly bitter
F2	Glossy, even shine, no streaks	Brown	Slightly bitter
F3	Glossy, even shine, no streaks	Brown	Slightly bitter
F4	Glossy, even shine, no streaks	Brown	Slightly bitter
F5	Glossy, even shine, no streaks	Brown	Slightly bitter

B. Physical Characteristics

Formulated chocolates were evaluated for Physical characteristics such as weight variation, hardness, thickness and disintegration time and the results are shown in table 6. Weight of chocolate was between 89-96mg. The hardness and thickness was in range of 2.1-3.1 kg/cm2 and 2.39-2.49 mm respectively.

Table No.6: Physical characteristics of Medicated chocolate.

Formulation code	Weight variation (mg)	Disintegration time	Hardness (kg/cm^2)	Thickness (mm)
F1	93.83 ± 0.2	80 sec ± 4.5	2.3 ± 0.01	2.42 ± 0.01
F2	92.29 ± 0.1	69 sec ± 3.6	2.1 ± 0.01	2.39 ± 0.01
F3	95.89 ± 0.1	55 sec ± 5	2.2 ± 0.02	2.47 ± 0.01
F4	89.23 ± 0.6	51 sec ± 1	2.4 ± 0.01	2.49 ± 0.02
F5	96.8 ± 0.6	35 sec ± 5	3.1 ± 0.03	2.49 ± 0.02

C. Determination of Drug content

The drug content of formulated chocolate was determined and results are shwn in table no. 7. The maximum drug content was found to be 98.47% in batch F5.

Table No. 7: Drug content.

Formulation code	Absorbance	% Drug content
F1	3.14	96.65 ± 0.05
F2	3.17	97.56 ± 0.02
F3	3.18	97.75 ± 0.05
F4	3.188	98.11 ± 0.02
F5	3.2	98.47 ± 0.02

D. In-vitro Drug release studies

Chocolates containg drug were evaluated for in vitro drug release studies and the results were given in table 8. Figure 2 depicts release profile of montelukast medicated chocolate.

Table No. 8: In-vitro perecent drug release.

TIME (mins)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	30.07	38.47	42.07	42.07	43.21
10	49.71	52.92	66.12	66.12	65.22
15	66.15	67.37	75.79	75.79	76.21
20	74.62	75.82	79.48	81.48	82
25	79.32	89.1	84.13	84.16	89
30	82.65	92.6	93.51	95.07	93.55

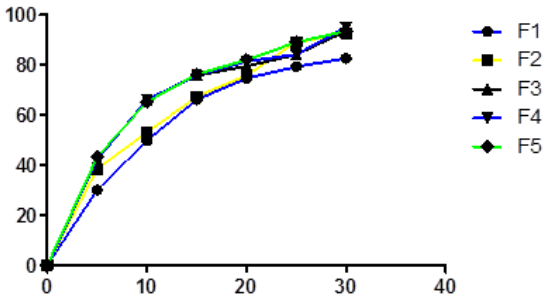

Figure No. 2: Drug release.

SUMMARY AND CONCLUSION

Chocolate is highly sophisticated a versatile food that is combined to create completely different taste and texture sensations. Medicated chocolate is prepared by using chocolate base and the drug is incorporated into prepared chocolate base.The medicated chocolate was prepared by using cocoa base and compound chocolate. Required amount of drug was weighed and added to the chocolate base and this mixture was poured to the silicon mould and kept for refrigeration. But a problem occurred when the chocolates were formed, the chocolates got melted within 5-10 mins at room temperature. To solve this problem, lecithin was added in different concentration. Preformulation study of drug was carried out. The prepared medicated chocolate were characterized for general appearance, weight variation, thickness, hardness, disintegration time, drug content and in vitro drug release.

Drug content of a medicated chocolate was determined by using UV Spectrometer. In vitro drug release was studied using USP II apparatus, with 500 ml of dissolution medium. The colour, odour, taste, and physical appearance of drug were observed visually.Study indicated that both the methods used in the formulation had similar drug release pattern. Batch F4 showed 95.07% at 30 mins whereas F5 showed 93.55% at 30 mins. The formulated chocolate was slightly bitter in taste but is a convenient form of dosage form for pediatrics. Lecithin used during formulation increased the hardness of chocolate.

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