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A RESEARCH ON FORMULATION AND EVALUATION CHEWING GUM OF SIMVASTATIN.

Tarade Vijay D.*, Chemate Satyam Z, Tushar Joshi V. and Kalyani Jadhav A.

Department of Pharmaceutics, P.D.V.V.P.F's College of Pharmacy, Vilad Ghat Ahmednagar (MS), India.

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***Correspondence for Author**
Tarade Vijay D.
Department of Pharmaceutics, P.D.V.V.P.F's College of Pharmacy, Vilad Ghat Ahmednagar (MS), India.

ABSTRACT

In present era, many research and technological advancements are made in the field of oral drug delivery as it is highly accepted amongst patient. In this research the formulation of antihyperlipidemic chewing gum of simvastatin using water insoluble gum base water soluble other portion containing drug as well as excipients like taste masking agent sorbital which use as a coating agent in this formulation. The primary and important requirement in the formulation of simvastatin chewing gum is the gum base, which give it gummy texture for chewing action and as a drug vehicle. This gum is isolated from the natural sources like a sapodilla monikara tree (Chiku) which fully grow in the Maharashtra region. This gum base have a property as like other gum bases which is present in nature. For the improvement in the stability of that gum base, which is converted in the dry form by drying and adding filler as talc and emulsifier such lecithin which was freshly collected from egg yolk. By drying this mixture further it convert in a directly compressible gum base powder, which possess all important flow property which require for direct compression. Direct compression is one of the best method as compare to moulding method in the formulation of chewing gum. For direct compression in directly compressible gum require other additional excipients like antiadherant, anti-caking agent, lubricant, antioxidant, flavor and sweetening, coating agent (sorbital). For evaluation of formulated chewing gum all parameter are same as like tablet except in-vitro drug release performance. For this purpose, the disintegration apparatus was modified in such way that it continuously compress or crush the chewing gum as like our mastication activity in the mouth, resulting in releases of drug in the salivary fluid and absorbance were calculate on UV-visible spectra. In this also study the effect of stroke &

distance between jaws which gives the valuable information about drug release performance in various ages patient.

KEYWORDS: Buccal delivery; Increased released, Hypertension, Stress.

1. INTRODUCTION

Definition of chewing gum

"Medicated chewing gum is solid, single dose preparation that has to be chewed and not swallowed; chewing gum contains one or more active ingredient that is released by chewing"

It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. Pharmacological active agents or drugs are formulated into variety of dosage forms like tablets, capsules, injectables, inhalers, ointments etc considering physicochemical properties, pharmacokinetic and pharmacodynamic parameters and biopharmaceutical aspects of drugs.[1] In addition to its confectionary role, chewing gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients.

A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue. Oral route is the most preferred route amongst the patient and clinicians due to various advantages it offers.

One of the reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Medicated chewing gum (MCG) is the gum base incorporating drugs.[2]

Chewing gum is being used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. One thousand years ago the mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen their breath. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today.[3] Chewing gum can be used as a convenient modified release drug delivery system. Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness and freshening of breath. In addition, a large number of chewing gum intended for prevention of caries, xerostomia and vitamin/mineral supplementation are currently available.

Chewing gum is a pleasure that almost everyone enjoys. Chewing gums are mobile drug delivery systems. Chewing gum usually consists of a gum core, which may or may not be coated. The water content of chewing gum is very low and requires no preservatives. Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as 'solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained. Generally, chewing gum is a combination of a water-insoluble phase, known as gum base and some other ingredients.[4]

These include powdered sugar whose amount and grain size determine the brittleness of the resulting gum, corn syrup and/or glucose which serve as humectants and coat the sugar particles to stabilize their suspension and keep the gum flexible, various softeners, food colorings, preservatives, flavorings etc.[5]

In his 1999 review of gum chewing and oral health. There are two absorption pathways which are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. Drug absorbed directly via the buccal membrane avoids metabolism in the G.I tract & the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum compared to other oral delivery system.[6]

2. MATERIAL AND METHOD

2.1 Excipients

Formulation of Directly Compressible Gum

Table.1. - Formula for Directly Compressible Gum.

Sr. No.	Ingredients	Wt. (gm)	Conce %	Use
1.	Natural Rubber Latex	40 gm.	40-70%	Provide elasticity & cohesion to chewing gum.
2.	Emulsifier's (Lecithin from Egg Yolk)	8 gm.	3-20%	Soften the Mixture & Give required chewability during mastication.
3.	Plasticizer's (Glycerol)	4.6 ml.	0.5 – 15%	It regulates the cohesiveness of product.
4.	Fillers, Talc	Q.S.		Provide right texture to gum base, improve chewability & provide reasonable size of the gum with low drug dose

2.3 Source of Material

Natural Rubber Latex From sapodilla tree

Figure. 1: Sapodilla Tree.

SAPODILLA

Monikara zapota

General Information.

Scientific name	**:**	*Manilkara zapota*
Pronunciation	**:**	man-ill-KAR-uh zuh-POE-tuh
Common name(s)	**:**	Sapodilla
Family	**:**	*Sapotaceae*

Description

Height	**:**	40 to 45 feet
Spread	**:**	35 to 45 feet
Crown uniformity	**:**	symmetrical
Crown shape	**:**	pyramidal, round
Crown density	**:**	dense
Growth rate	**:**	moderate
Texture	**:**	coarse

Culture

Light requirement	**:**	full sun
Soil tolerances	**:**	clay; sand; loam; alkaline; Acidic; well-drained

Drought tolerance : high

Aerosol salt tolerance: high

A uniquely flavored fruit, the soft brown flesh of the sapodilla tastes a bit like a sweet mix of brown sugar and root beer. The sapodilla tree is also the source of chicle, a chewing gum component.

1. Description

A slow growing and very large tree that can reach over 100 ft in the tropics. Fruiting occurs 4-6 months after flowering, with fruit sometimes ripening in bunches multiple times of the year.

2. Hardiness

The sapodilla is reasonably hardy tree when full grown and can stand temperatures into the high 20's.

3. Growing Environment

Grow in full sun. Trees are at home in both dry and wet climates and are drought tolerant.

4. Uses

Eaten fresh, usually as a dessert fruit. The bark contains a gummy latex substance called chicle which used to be a primary ingredient in chewing gum.

5. Propagation

By seeds or grafting. Seeds can remain viable for several years.

Steps Involve in Isolation of Chicle /Gum From Natural Source

Fig. 2: Steps Involve in Isolation of Chicle /Gum From Natural Source.

Source of gum /Chicle

Binomial name ***Manilkarazapota***

Sapodilla (Sapota) nutrition facts

Sapodilla or sapota (*chikoo)* is another popular tropical fruit in line with mango, banana, jackfruit, etc. Sapota composes of soft, easily digestible pulp made of simple sugars like fructose and sucrose.

Sapota is a tropical evergreen, fruit-bearing tree belongs to the family of *Sapotaceae,* in the genus: *Manilkara*. Scientific name: Manilkarazapota.

Procedure

Weigh all the above ingredient in require quantity. Frist take the rubber lates which is obtained from "Sapodilla Monikara" tree / Chicle / Chikka, by inserting a steel /hard glass capillary in smooth trunk of the tree.

Attach a small size container at the tip of capillary. The white color sticky gum is start collected in a container.

In 24 hr's we get 1-3 gm of rubber latex.

Take this rubber latex in a clean & dry metal dish & heat or melt the gum base on water bath. Then add in it emulsifier lecithin which is freshly collected from Egg – Yolk by maintaining Temp 60^0c for 45 min.

The lecithin get mix with rubber latex & Solution which is very sticky is from. Then in it add a glycerol to decrease the stickiness of gum which helps in formation of non sticky mass of gum.

Then add in it Talc as a filler which provide right texture; and also provide reasonable size of the gum lump with low dose drug.

Pass the above mixture from sieve no12#, 24 # and finally 100 #.

Store the above gum mixture in Amber colored glass bottle to avoid the degradation and improve stability [7]

Emulsifier's (Lecithin from Egg Yolk)/ it is a lab scale preparation procedure.

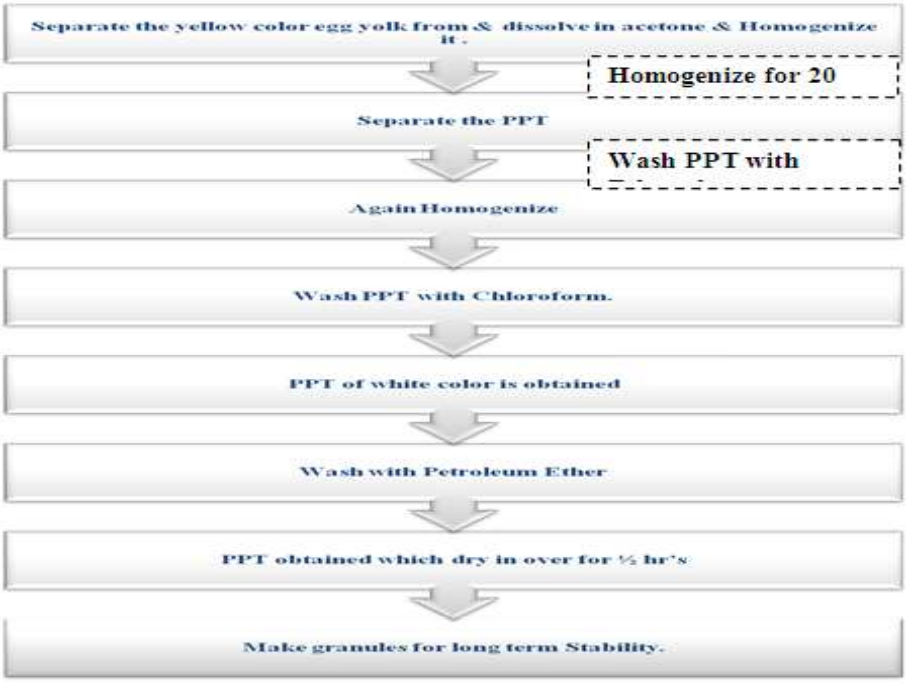

Figure 3. - Detail Procedure for isolation of lecithin from egg yolk.

Formula

Tabl. 2. Formula for Simvastatin Chewing Gum.

Sr .No	Ingredients	Quantity	Use
1.	Directly Compressible Gum	350 mg	Vehicle
2.	Simvastatine	20 mg	Anhyperlipidemic Drug
3.	Carbopol -934	320 mg	Polymer
4.	Na –CMC	64 mg	Stabilizer, Thickening Agent
5.	MCC	10 mg	Anti-Caking Agent
6.	Magnesium Stearate	2 mg	Lubricant
7.	Citric Acid	2 mg	Antioxidant
8.	Pineapple Flavor	Q.S	Flavor
9.	Sorbital	Q.S	Sweetening, Coating Agent

Detail Procedure :- (By Direct Compression)

Fig.4: Direct Compression Technique for Chewing gum Formulation.

1. Weigh all the Ingredients Accurately.
2. Pass the Ingredients through Sieve no .100 except Lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min.
3. After sufficient mixing lubricant was added and again mixed for 2-3 min.
4. The mixture is compressed using 12 mm flat faced punch.

Procedure for Sugar Coating of Chewing Gum

Fig 5. Sugar Coating of Chewing Gum.

1). Directly Compressible Gum: - As above procedure directly compressible gum can be prepared.

2). Simvastatine (API):- From Wok hart Pharmaceuticals Aurangabad as a gift sample.

Drug Profile

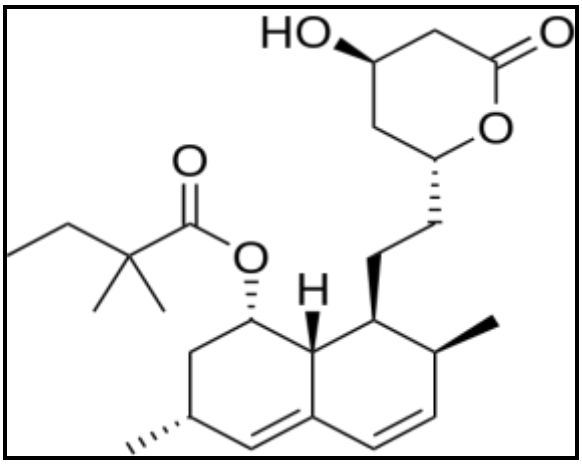

Fig. 6: - Structure of Simvastatin.

- **Name : Simvastatin**
- **Description : used to treat heart diseases**
- **Categories : use in Hypercholestemia /HMG-CoA reductase**
- **Weight : 418.566 g/mol**
- **Chemical Formula :** $C_{25}H_{38}O_5$
- **Classes : Antihyperlipidemic**
- **Dose : Adult 5-40 mg, Children-10 mg/ day**
- **Solubility :**

Solvent		mg/ml
Methanol	**:**	**200**
Ethanol	**:**	**160**
Water	**:**	**0.03**

Plz Note that: - (Following Chemical are very common which is used in tablet and dosage form formulation).

3). Carbopol -934:- As a gift sample from ALPHA CHEMIKA SAVGAN HEIGHTS, 102, B WING, RTO LANE, ANDHERI (WEST), Mumbai - 400053, Maharashtra, India.

4) Na –CMC: - Triveni Aromatics and Perfumery Private Limited.

5) Glycerol (as a plasticizer):- From Ashok Chemical Agency Pvt ltd, Ahmednagar.

6) Talc as filler:-from Chaitanya chemicals, Pune.

7) MCC: -Yogi Dye Chem. Industries.

8) Magnesium Stearate:-A. B. Enterprises No. 202, Shradanand Building, No. 272/ 274, Samuel Street, Mumbai - 400003, Maharashtra.

9) Citric Acid:- Deshmukh Chemicals No. 2, Anupam Plaza, Near Rajmata Karyalaya, Meri Adgaon Link Road, Nasik - 422004, Maharashtra.

3. RESULT AND DISCUSSION

Preformulation of Directly Compressible Gum

Physical Properties

Total weight of powder = 20.20 gm

Flow Properties

Table. 3: Preformulation of Directly Compressible Gum.

Formulation Batch Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ration	Angle of Repose(Degrees)
B1	0.5941	0.7769	23.52	1.3076	21.80
B2	0.5789	0.6811	21.88	1.2136	24.55

4. Evaluation of Formulated Chewing gum

(In evaluation of chewing gum there are some short and few methods of evaluation which is as below).

A) Physical Evaluation

1) Hardness

Hardness or crushing strength is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto Hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel at which the tablet fractures indicates the hardness of the tablet. Six tablets from each batch were taken randomly and their hardness was determined.

3) Thickness (mm)

Thickness was determined for twenty pre-weighed tablets of each batch using a digital venire scale and the average thickness was determined in mm**.** The tablet thickness should be controlled within a 5% variation of a standard.

4) Friability

Thickness was determined for twenty pre-weighed tablets of each batch using a digital venire scale and the average thickness was determined in mm**.** The tablet thickness should be controlled within a 5% variation of a standard.

5) Stickiness

Chewing gum placed on plane surface, 250 gm cylinder hammer collide on to it for periods of ten minutes. The frequency of hammering was about 30 per minute. After 10 min., Sticking of mass to hammered surface was observed and reported.

Physical Evaluation

Table. 4: Physical Evaluation.

Formulation	Color	Thickness mm	Friability %	Hardness kg /cm ^{2}	Stickiness	Weight mg
B1	White	12.0	0.54	3.1	Non	1.1
B2	White	13.0	0.75	2.9	Non	1.12

Chew out study

In this study the effect of force acting on chewing gum, temperature, twisting angle and distance between jaws are to be study [15].

In vitro Drug release based on

- Change in twisting angle of upper mastication jaw from (50-30^0).
- Change in distance b/w upper and lower masticating Jaw from (1-2 mm).
- Change in chewing frequency of lower masticating Jaw from (20 strocks / minute to 120 strokes / minute).

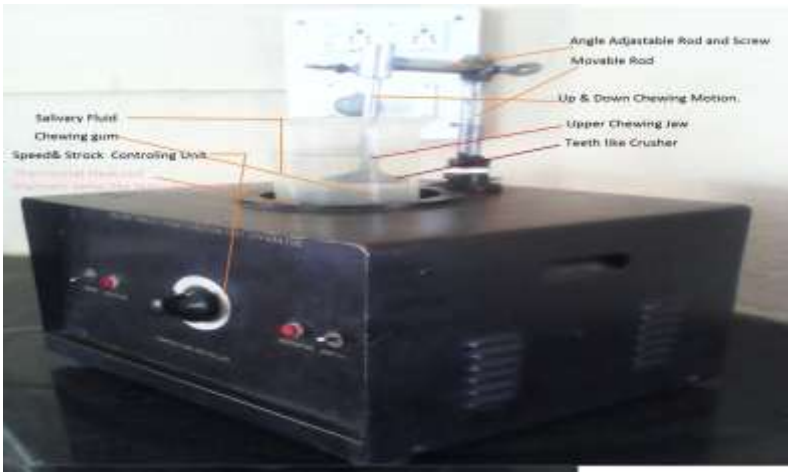

Fig 8. Chewing Gum In vitro Drug release Apparatus.

In-vitro release test was performed using lab fabricated medicated chewing gum apparatus. The disintegration test apparatus was modified in such a way that the formulation was pressed continuously like mastication process. From the *in vitro* drug release data it was concluded that drug release from the medicated chewing gum was satisfactory.

The chewing gum was inserted between the pistons on to the chewing surface. The chewing procedure consisted of up and down stroke of lower masticating surface combined with twisting movement of upper masticating surface, thereby masticating the chewing gum and consequently agitating the test medium. The optimized chewing frequency employed in the

study was 60 -+ 2^0 stroke per minute. At predominant time interval aliquot of the artificial saliva, were removed and assayed for drug content by UV spectrophotometric Analysis [16]. The release medium was replaced with fresh artificial saliva after each sample was taken.

On setting 20^0 (which is optimized setting for twisting angle) as twisting angle movement for upper masticating jaw after, 45 min. 99% drug release was noted, which emphasize that increasing twisting angle increase rate of release of drug significantly. It was noted that for optimized formulation that as we decreases the distance between the upper and lower masticating surface from 2 mm to 1 mm, this lead to increases in rate of release since the force acting on the gum is larger with 1 mm setting [17]. When distance between Jaws increase from 1 mm to 2 mm for MCG % drug release decrease and time interval needed for drug release increase. Chewing frequency of lower masticating Jaw is important factor in the mastication process. As we increase the frequency of chewing or movement of lower masticating jaw the drug release profile shows significant increases [18]

As we increase the number of frequency of the lower masticating jaw the release profile of drug show increase in lower time interval . High kneading speeds between in the time interval for release is obtained.

Calibration Curve

Table. 5: Calibration Curve.

0	0
2	0.1909
4	0.3701
6	0.4974
8	0.7053
10	0.8651

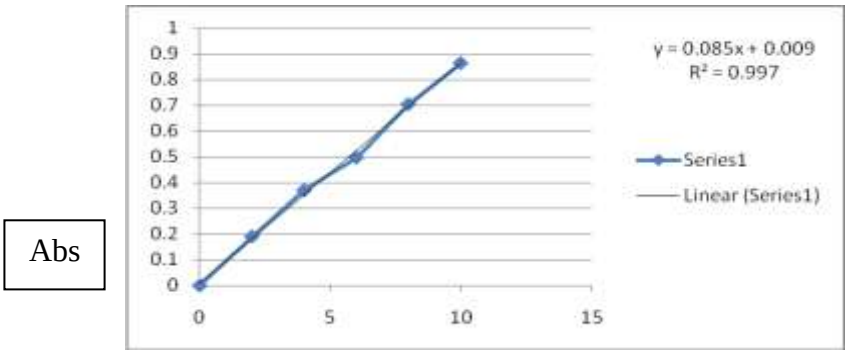

Fig. 9: Calibration Graph.

Methanol 2ppm.

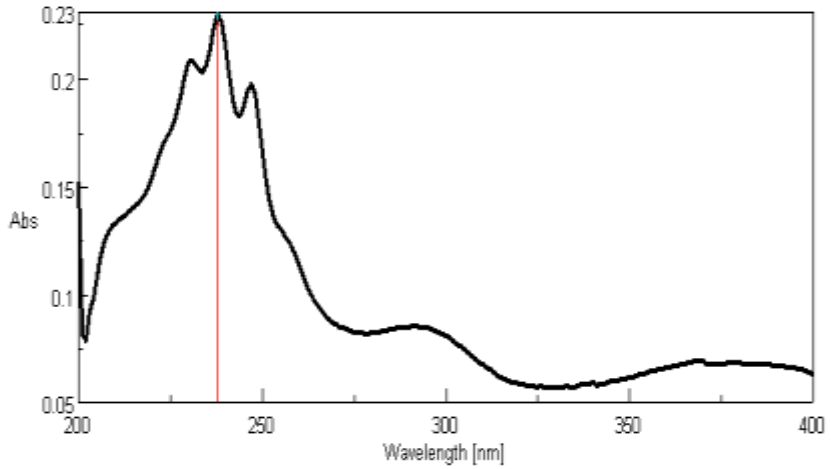

Fig. 10: U .V Spectra of API.

Table. 6: - In Vitro drug release with setting of chewing Frequency 60 Strokes /min.

Sr. No	Chewing Frequency (Strokes /min)	Time Interval (min)	Cumulative % Drug Release
1	60	0	0.000
2	60	2	23.658
3	60	4	45.756
4	60	6	73.722
5	60	8	82.767
6	60	10	84.380
7	60	12	90.282
8	60	14	93.684
9	60	16	96.825

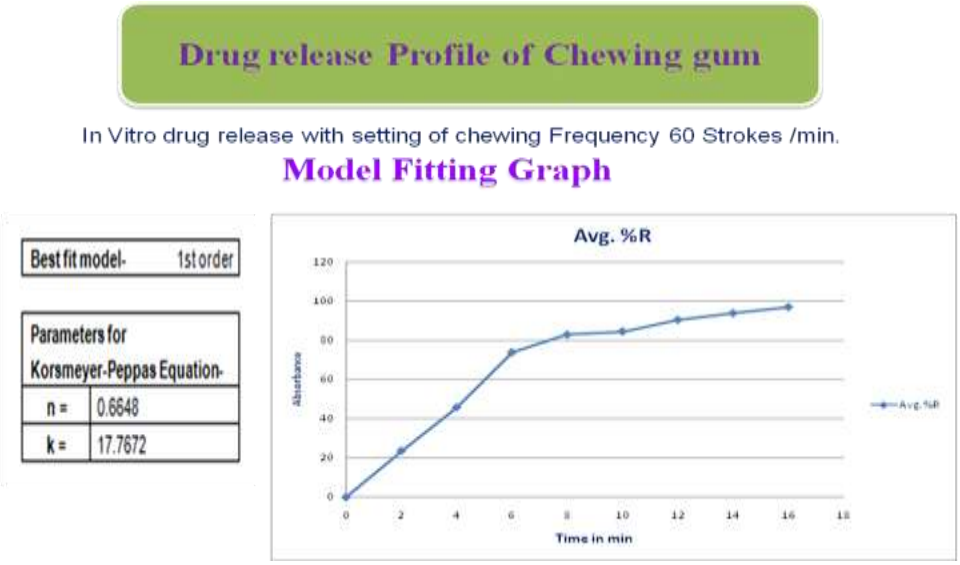

Fig. 11: In Vitro drug release with setting of chewing Frequency 60 Strokes /min.

Table. 8: - In Vitro drug release with setting of Distance between the Jaws 1.5 mm.

Sr. No	Distance Between Jaws (mm)	Time Interval (min)	Cumulative % Drug Release
1	1.5	0	0.000
2	1.5	2	10.774
3	1.5	4	18.094
4	1.5	6	26.689
5	1.5	8	34.451
6	1.5	10	42.610
7	1.5	12	50.375
8	1.5	14	56.337
9	1.5	16	63.425
10	1.5	18	68.300
11	1.5	20	74.298

It was noted that, decreasing the distance b/w the upper and lower masticating surface from 2 mm to 1 mm lead to increase in the rate of release since the force acting on the gum is larger with 1 mm setting.[17]When distance between Jaws increase from 1 mm to 2 mm for MCG, % drug release decreases while time interval needed for drug release increases.[18]

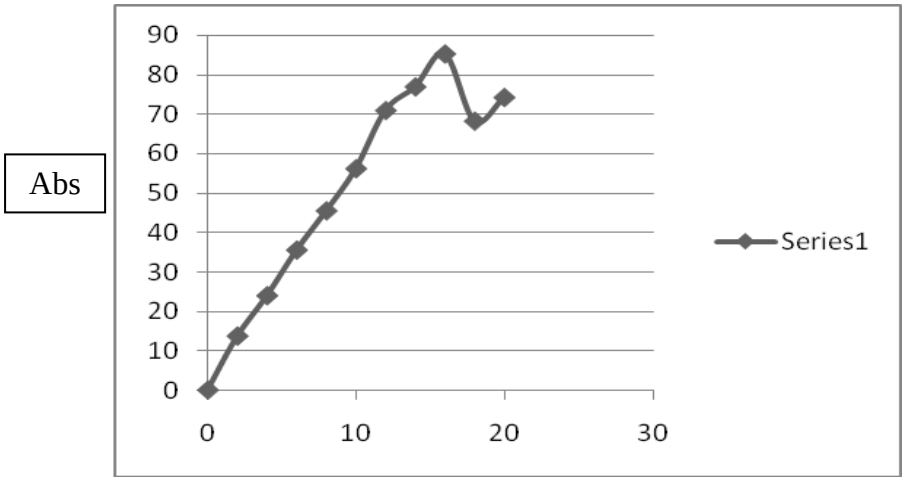

Fig.12:- In Vitro drug release with setting of Distance between the Jaws 1.5 mm.

Stability Studies

Table. 9:- Stability Studies.

Sr. No	Properties	Observation
1	Color (before ageing)	White to off white
2	Color (after ageing)	White to off white
3	Softening range (before ageing)	75 to 85^{0}C
4	Softening range (after ageing)	75 to 85^{0}C
5	Texture (before ageing)	Gummy
6	Texture (After ageing)	Gummy

IR Study (For Compatibility)

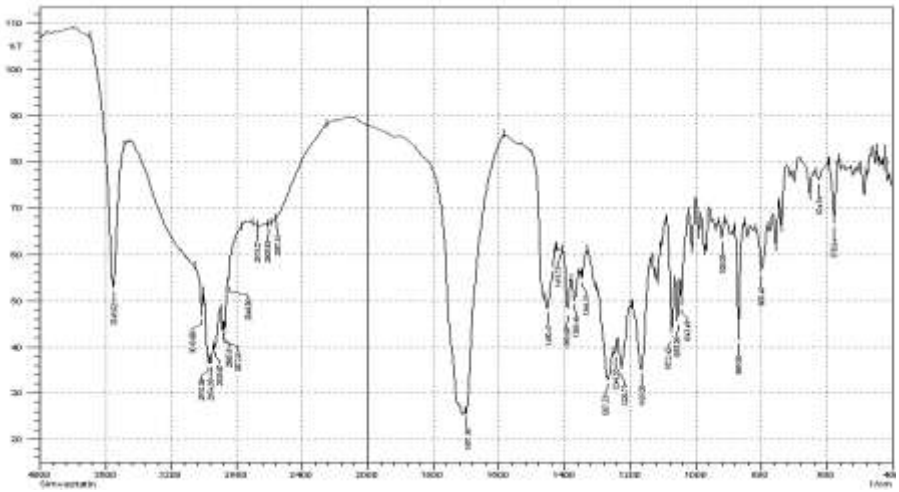

Fig. 13: - IR of API.

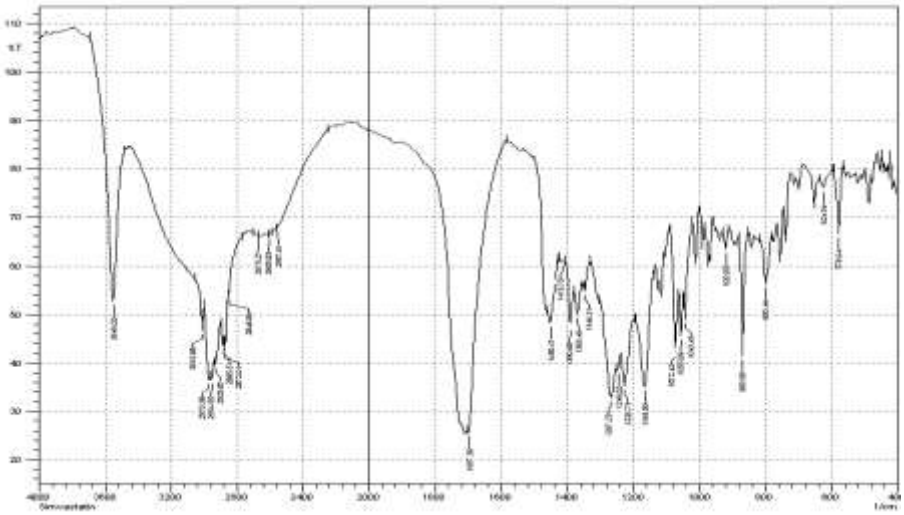

Fig. 14: IR of Formulation.

Table. 10: IR ranges with functional group Matching.

Functional groups	C=O Ketone	Aldehyde	N-CH_3	Alkane (stretching)	H-bond bet^n OH gr.	CH_2 group
Frequency (cm-1)	1697	1724	1421	2780-3000	3550	1340-1400

CONCLUSION

The present work was aimed to develop the medicated chewing gum as drug delivery system for simvastatin with fast onset of action and to avoid first pass metabolism. Chewing gum formulations were prepared using synthetic gum base and different plasticizers such as glycerin and lecithin as an emulsifier. MCG formulations were evaluated for different parameters like stickiness, weight variation, percent drug content and *in vitro* drug release test were performed. *In-vitro* release test was performed using lab fabricated medicated

chewing gum apparatus. The disintegration test apparatus was modified in such a way that the formulation was pressed continuously like mastication process. From the *in vitro* drug release data it was concluded that drug release from the medicated chewing gum was satisfactory.[14] Percent drug release of all formulation batches is in between 46.49% to 96.45%.

FUTURE TRENDS

Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. A few decades ago, the only treatment for some disease was surgical procedure but now more and more disease can be treated with Novel Drug Delivery Systems. Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients; however chewing gum is believed to manifest its position as a convenient and advantageous drug Delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances.[13] The potential of MCG for Buccal delivery, fast onset of action and the opportunity for product line extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

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