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A Study on Taste Masked Valsartan Containing Chewing Gum

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ABSTRACT

Now a day's, many research and technological development are made in the field of oral drug delivery as it is highly suitable amongst patients. In this research the formulation of antihypertensive chewing gum of valsartan using different plasticizers. Valsartan has low bioavailability, bitter taste and also it is affected by hepatic first-pass metabolism. So it is important to avoidance of all of these drawbacks valsartan chewing gum was prepared. Valsartan is sparingly soluble in water and bitter taste due to poor solubility; improvement of solubility of valsartan was carried out by complexion technique. Valsartan and β-cyclodextrins inclusion complex were formulated in the mortar and pestle kneading method. Medicated chewing gum was prepared for valsartan with direct compression method using, glycerol and castor oil as a plasticizer and it is evaluated for different parameters.

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INTRODUCTION

Medicated chewing gum

The medicated chewing gum is solid, single-dose preparation with a base consisting mainly of gums that are intended to be chewed, but not swallowed. It contains one or more active substance which is released by chewing action and it is used for local treatment of mouth disease on systemic delivery after absorption through the buccal mucosa.

As a drug delivery system chewing gum has many advantages over another administration form; its main attributes include its convenient manner; being able to chew discreetly at any time and any place and no requirement of water. (6)

Hypertension is known as high blood pressure (HBP) usually does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for Coronary Artery Disease, Stroke, Heart Failure, Arterial Fibrillation, Peripheral Vascular Disease, Vision Loss, Chronic Kidney Disease and Dementia. (14)

Valsartan angiotensin-II receptor antagonist used in the management of hypertension. It may also be used in a patient with heart failure who are unable to tolerate ACE inhibitors. Valsartan lowers blood pressure by antagonizing Renin-Angiotensin-Aldosterone System (RAAS), it competes with angiotensin-II for binding to the type 1 and angiotensin-II receptor (AT_1) subtype and prevents the blood pressure increasing effect of angiotensin-II. (26-27)

Valsartan is classified as Biopharmaceutical Classification System (BCS) class II, The drug that have low solubility and permeability characteristic after oral administration use of cyclodextrins is one of the pharmaceutical strategies available to circumvent these drawbacks, as they can be used as a complexing agent to increase the aqueous solubility of hydrophobic drugs and to increase their bioavailability and stability.

MATERIALS AND METHODS

MATERIALS

Valsartan was provided as a gift sample from Kusum Healthcare Pvt. Ltd, Gurgaon Delhi. Polymers and excipients such as Bees Wax, Castor Oil, Glycerol, Propylene Glycol, Dextrose, Calcium Carbonate, Polyvinyl Pyrrolidone, Mannitol, Magnesium Stearate,

Aerosil,β –cyclodextrin, etc. were purchased from S D Fine Chm. Pvt. Limited, Merck Specialties Pvt. Limited, Fisher Scientific.

METHODS:

Solubility Enhancement of Valsartan by Complexation with β-Cyclodextrin.

Preparation of inclusion complex by kneading method:

Preparation of inclusion complex of Valsartan and β-cyclodextrin, molar concentration 1:1 was taken. In the kneading method, a mortar was wetted with a sufficient amount of water (10% w/w) to obtain a paste and Valsartan was slowly added to the paste. Kneading was performed manually for an hour and a suitable amount of water was added from 100 time to time to maintain the consistency of the paste. The mixture was dried overnight for 24 hr in an oven at 50°C. The dried complex was ground using mortar and pestle. After sieving through a #65 mesh sieve, the inclusion complex was kept in a closed container.

Formulation of Medicated chewing gums

Method of Preparation of medicated chewing gums by direct compression Method

Medicated chewing gums of Valsartan were prepared by direct compression method by using beeswax, glycerol, propylene glycol or castor oil as plasticizers. All the ingredients including drug, plasticizer and all other excipients were weighed accurately according to the batch formula. The drug and all the ingredients were mixed and blended for 10 min in an inflated polyethylene pouch. The prepared blend of each formulation was compressed by using a compression machine.

Table No. 1: Formulation table

Sr.no.	Name of Ingredient	Formulation						
		F1PG	F2PG	F3PG	8F4G	F5G	F6C	F7C
1	Bees wax	136	136	136	136	136	136	136
2	Propylene glycol(mg)	80	120	160	_	_	_	_
3	Glycerol(mg)	_	_	_	120	160	_	_
4	Castor oil(mg)	_	_	_	_	_	120	160
5	Dextrose	81.35	81.35	81.35	81.35	81.35	81.35	81.35
6	Calcium carbonate	81.35	81.35	81.35	81.35	81.35	81.35	81.35
7	Polyvinyl pyrrolidone	68	68	68	68	68	68	68
8	Mannitol	642	642	642	642	642	642	642
9	Peppermint oil(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	Magnesium Stearate	4	4	4	4	4	4	4
11	Aerosil	10	10	10	10	10	10	10

Evaluation of Medicated Chewing Gums:

1. Hardness test

After formulating the preparation, they may require certain strength, so the hardness of medicated chewing gums was measured using Monsanto Hardness Tester and expressed in kg/cm^2.

2. Thickness

The thickness of randomly selected medicated chewing gums from each formulation series was determined in mm using a Screw gauge.

3. Friability test

The prepared six medicated chewing gums were randomly taken, they were weighed and placed in the friabilator and rotated for 100 revolutions for 4 min. and then formulations were taken out from the friabilator, dedusted and reweighed, determine the % loss using the following formula.

% loss = initial weight – final weight /initial weight ×100 %

Friability of tablets less than 1 % is considered acceptable.

4. Uniformity of weight

The weight variation test was determined by randomly selecting 20 medicated chewing gums, their weights are determined using electronic balance initially and the average weight was calculated from the total weight.

5. Colour

The Colour of prepared medicated chewing gums of all formulations was Observed visually.

6. Stickiness

The prepared medicated chewing gums are placed on the plain surface, Teflon hammer weight of 250 gm colloid on preparations for 10 min, after 10 min sticking of mass to hammered surface was visually observed.

7. Uniformity of drug content [34]

Five medicated chewing gums were powdered in a mortar and the powder equivalent to 10 mg of drug was placed in a stoppered 100 ml conical flask. The drug was extracted with 40 ml distilled water with vigorous shaking on a mechanical shaker (100 rpm) for 1 hour. Then heated on a water bath with occasional shaking for 30 min and filtered into 50 ml volumetric flask, the filtrate was made up to the required volume bypassing more distilled water through the filter, dilutions were made and absorbance was determined at specific wavelength using UV spectrophotometer against blank.

8. Method development of dissolution apparatus for studying the release of drug from Medicated Chewing Gums [35]

Upon the extensive literature survey, the disintegration apparatus was slightly modified. The apparatus consists of a beaker of 1000 ml capacity and two rods welded with two plates attached to the apparatus main stand, which acts as a lower chewing surface and an upper chewing surface. The chewing gum was placed on the lower surface and there is a provision to move the upper surface of the rod towards upward and downward motion at a chewing

frequency of 60 strokes per minute and observe for the drug release in 6.8 pH phosphate buffer for 30 min to ensure the maximum drug release from the formulation.

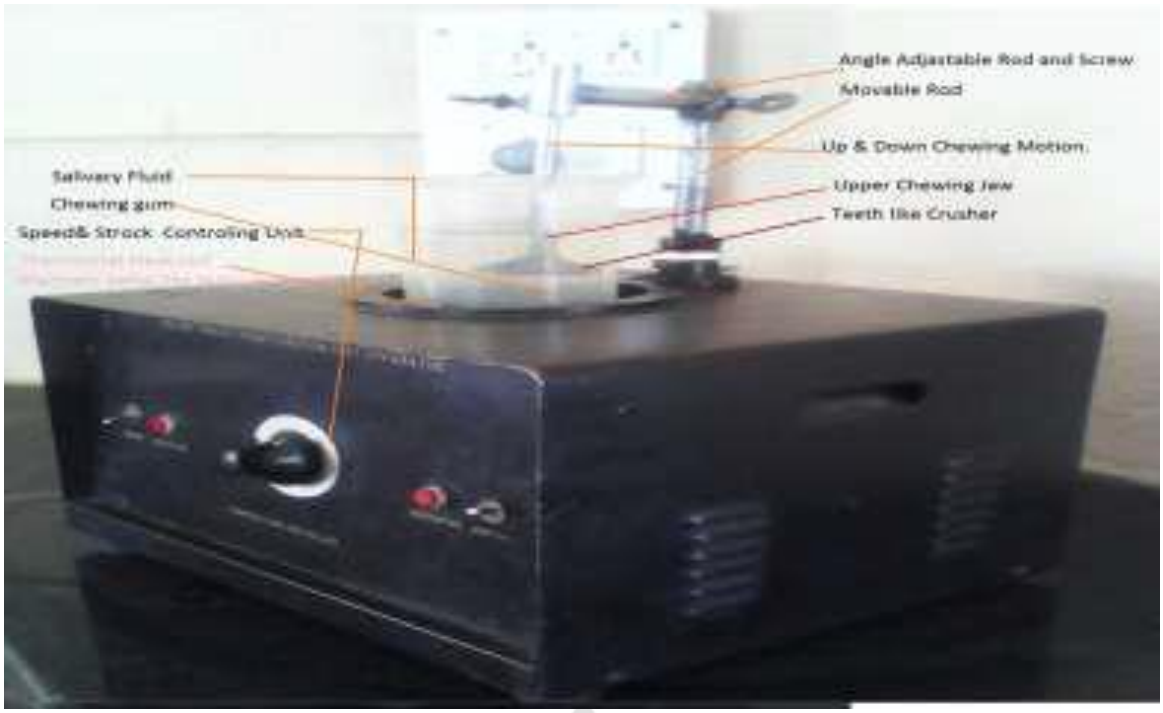

Figure No. 1: Modified *in vitro* dissolution apparatus

9. *In-vitro* drug release study

The study was carried out in a modified dissolution apparatus with 500 ml of phosphate buffer pH 6.8 as dissolution medium is taken in a beaker and maintained at 37± 0.5 0C. The prepared chewing gums are placed in apparatus, at different time intervals like 5, 10, 15, 20, 25, 30 min, 5 ml of sample was withdrawn and replaced with fresh medium. All experiments were done in triplicate and average values were taken. The samples were filtered through 0.25 µM membrane filter paper and analysed for drug concentration after appropriate dilution at a specific wavelength using a UV-Visible spectrophotometer.

10. Stability Studies

Stability studies were performed according to the ICH guidelines. [97] The prepared medicated chewing gums were kept in the stability chamber at a temperature of 25° C/60 % RH and 40° C/75 % RH for 6 months. At the end of 6 months, samples were withdrawn and observed for physical appearance and investigated for % drug release.

RESULTS AND DISCUSSION

1. Melting Point Determination

The melting point was observed in the glass capillary tube which was sealed at one end. The melting points were found to be in the range of 160°C to 165°C.

2. Calibration Curve of Valsartan

The standard calibration curve shows the slop of 0.0449 and a correlation coefficient of 0.9999. The curve was found to be linear concentration rang 5, 10, 15, 20µg/ml at 250 nm. The calculation of drug content, In-vivo dissolution study was based on the calibration curve.

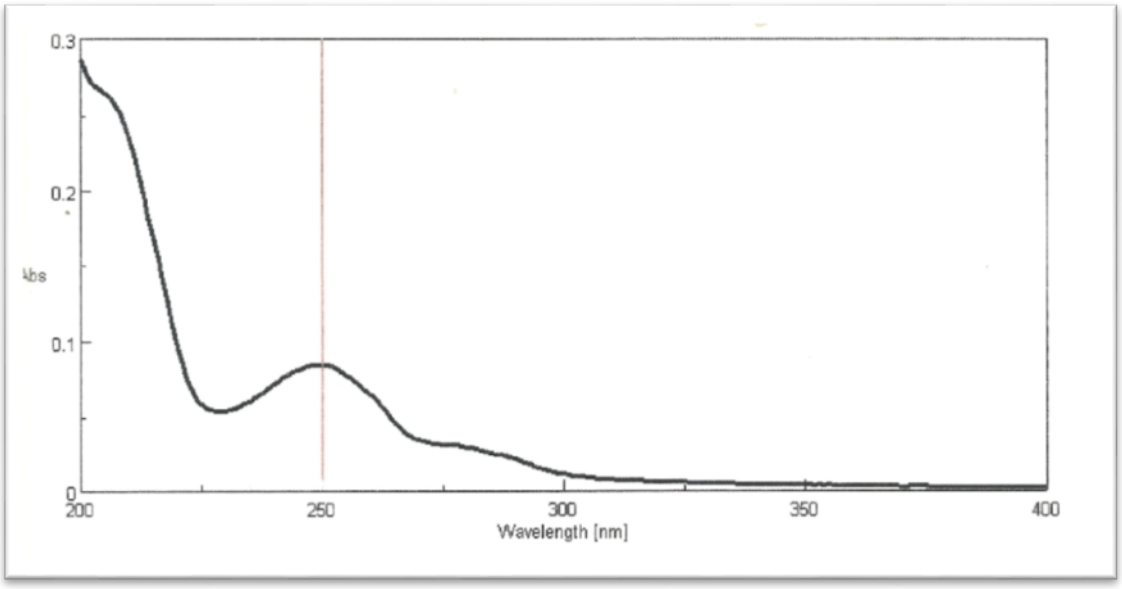

Figure No. 2: UV Spectrum of Valsartan

Table No. 2: Standard graph of valsartan in pH 6.8 artificial saliva

Sr. No.	Concentration(µg/mL)	Absorbance at 250nm
1	0	0
2	5	0.2228
3	10	0.4510
4	15	0.6798
5	20	0.8944

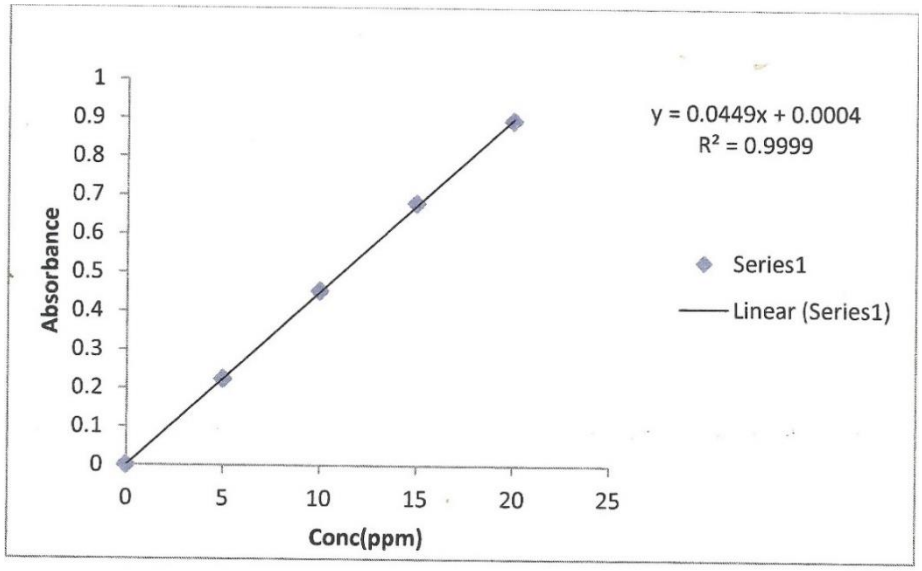

Figure No. 3: Calibration Curve of Valsartan in pH 6.8 artificial saliva

Compatibility Studies

3. DSC Analysis

The DSC thermogram of Modafinil showed a sharp endothermic peak at 107ºC. The DSC thermogram optimized formulation showed an endothermic peak at 145.05ºC. It indicates that there was no interaction found between drug and all other excipients used in the formulation of medicated chewing gum of Valsartan.

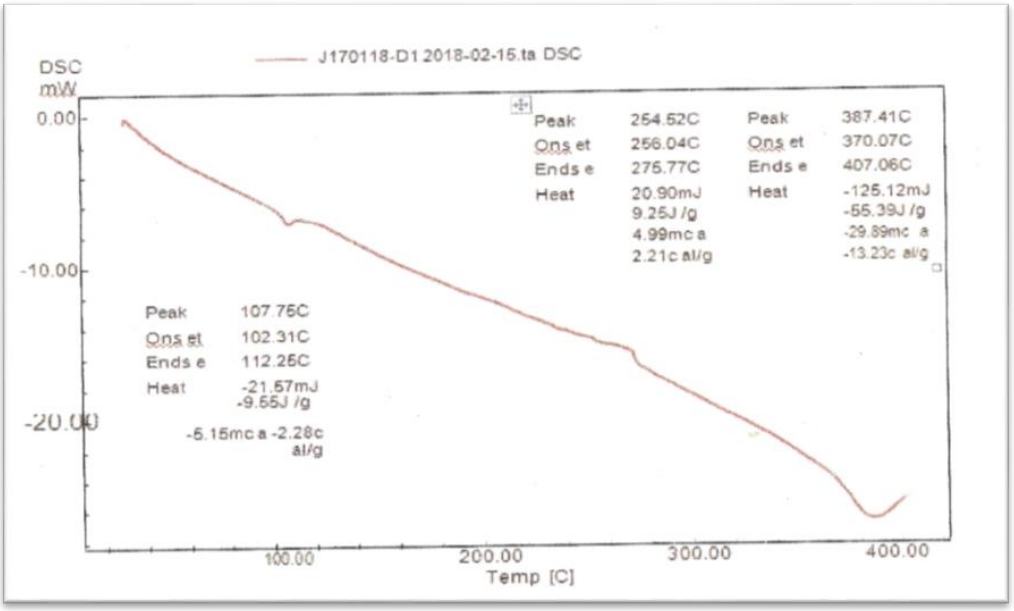

Figure No. 4: DSC of pure drug

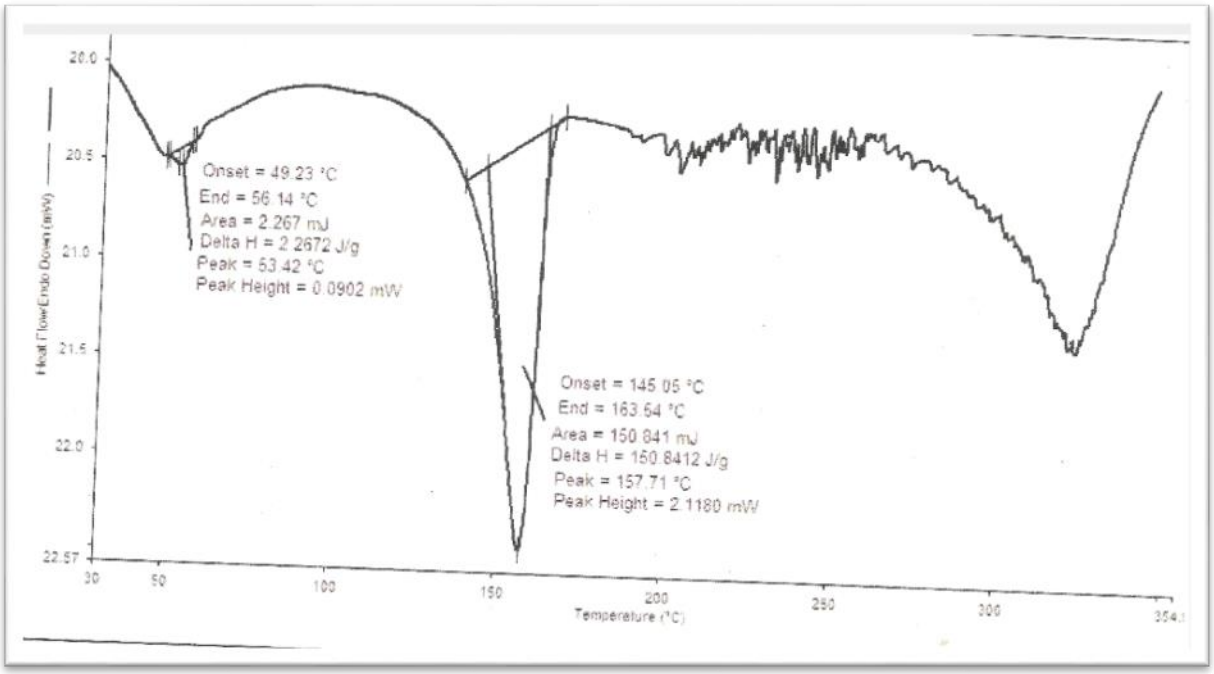

Figure No. 5: DSC of optimized formulation using castor oil as a plasticizer

4. FTIR Spectral Analysis

To study the interaction between drug and excipients used in the development of medicated chewing gums, IR spectroscopy was carried out.

Table No. 3: FTIR Spectral data of Valsartan and optimized formulation

Group	Wavenumber (cm-1)			
	Pure drug	FPG4	FG5	FCA6
RCOOH	1732	1669.69	1849.04	1847.47
O-H	2962	2650.68	2766.19	2774.1
=CH-H	1409.96	1317.14	1332.4	1342.21
N-H	1598.99	1517.7	1556.27	1556.27
C-H	777.31	793.56	770	777.82

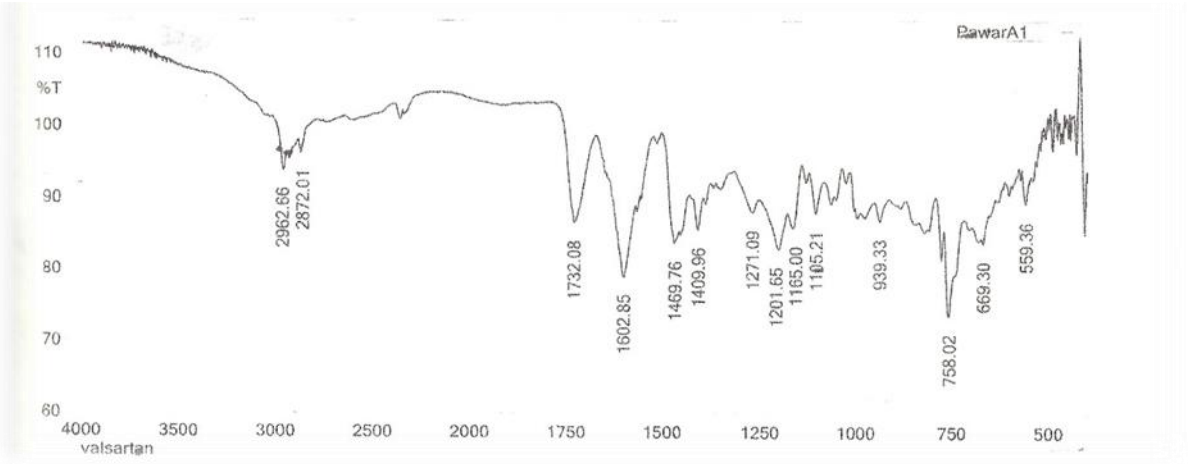

Figure No. 6: IR of pure drug

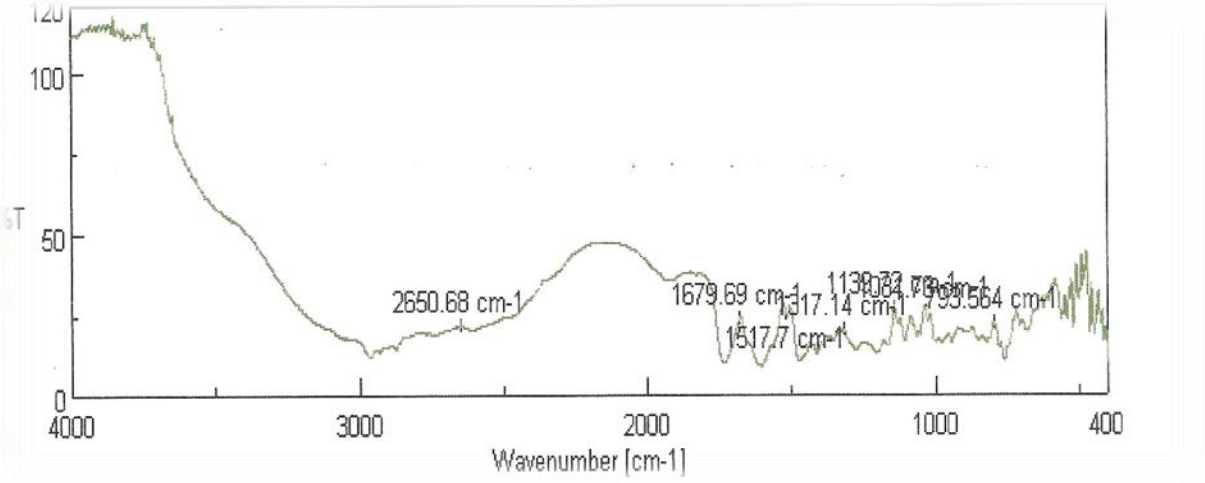

Figure No. 7: IR formulation using Propylene glycol as plasticizer

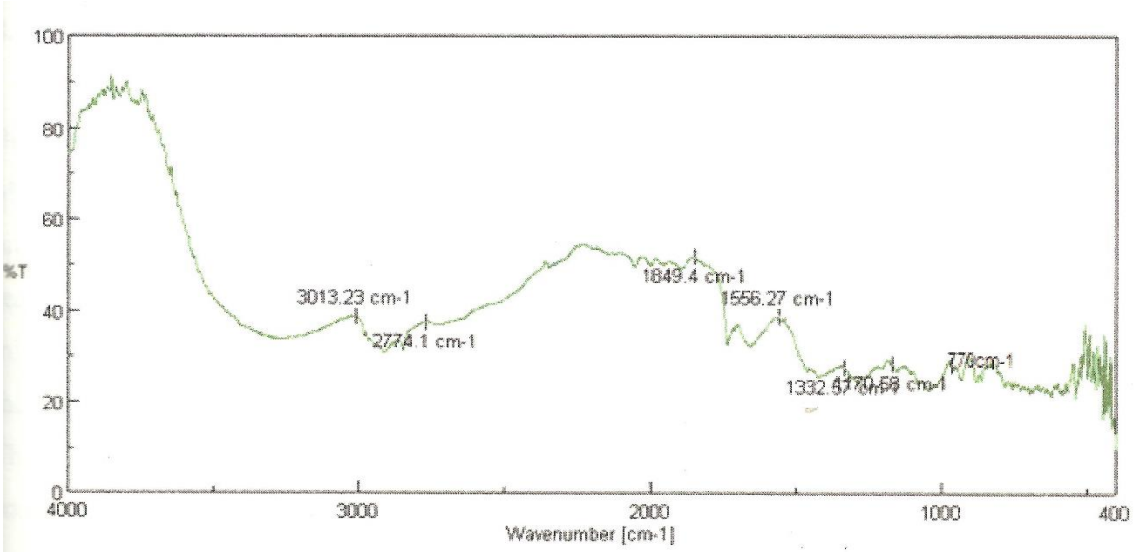

Figure No. 8: IR of formulation using Glycerol as plasticizer

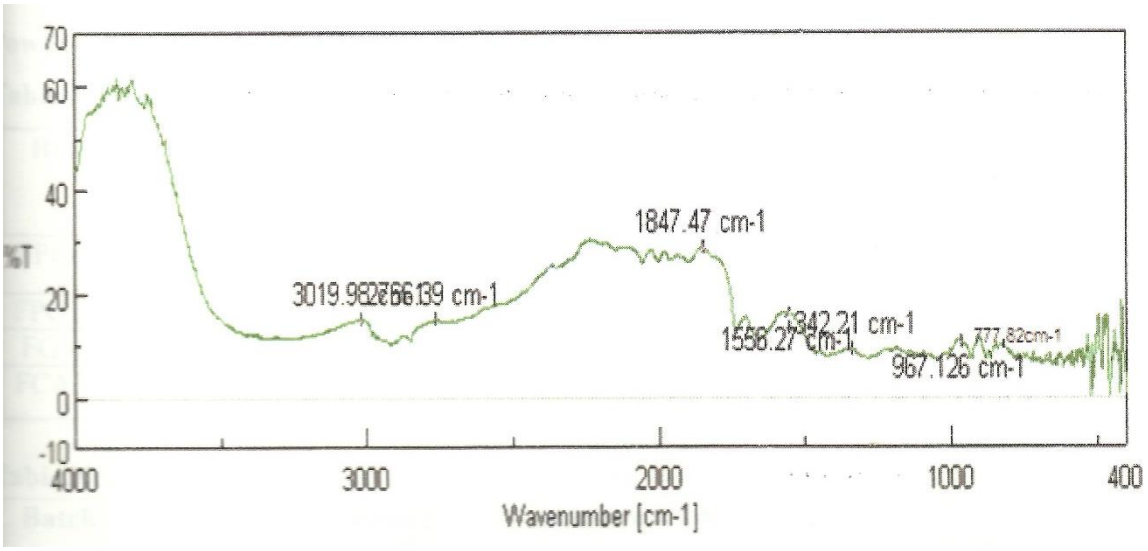

Figure No. 9: IR of formulation using Castor Oil as a plasticizer

5. Powder blend precompression evaluation

For each type of preliminary formulation blend, blends of API and excipients were prepared and evaluated various parameters as explained earlier.

Table No. 4: Physical parameters of powder using concentration 120mg of plasticizer

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	% Compressibility	Hausner's Ratio	Angel of Repose(Ɵ)
$FPG0_{(80)}$	0.584±0.02	0.622±0.0026	6.54±0.036	1.08±0.05	27º78'±0.097
$FPG1_{(120)}$	0.588±0.03	0.630±0.044	6.25±0.020	1.08±0.11	28º72'±0.067
$FG3_{(120)}$	0.590±0.02	0.634±0.027	5.03±0.021	1.09±0.12	26º84'±0.051
$FCA3_{(120)}$	0.594±0.03	0.649±0.028	4.9±0.061	1.05±0.098	28º68'±0.054

Table No. 5: Physical Parameter of powder using concentration 160mg of plasticizer

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	% Compressibility	Hausner's Ratio	Angel of Repose (Ɵ)
$FPG_{(160)}$	0.567±0.18	0.608±0.024	6.40±0.060	1.06±0.032	28º85'±0.025
$FG5_{(160)}$	0.571±0.17	0.598±0.030	6.55±0.045	1.07±0.046	29º93'±0.041
$FCA6_{(160)}$	0.578±0.24	0.617±0.027	6.35±0.022	1.10±0.055	27º86'±0.068

Physical parameter of Valsartan medicated chewing gums using different concentrations of PEG, PG, and castor oil.

Table No. 6: Physical Parameter of Formulations using concentration 120mg of plasticizer

Batch	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug Content (%)
$FPG0_{(80)}$	2.10±0.22	0.73±0.12	0.30±0.015	1298±0.03	97.99±0.03
$FPG1_{(120)}$	3.4±0.16	0.72±0.13	0.25±0.023	1300±0.16	98.33±0.16
$FG3_{(120)}$	3.3±0.22	0.75±0.12	0.22±0.016	1299±0.03	97.89±0.12
$FCA3_{(120)}$	3.6±0.218	0.73±0.15	0.21±0.023	1299±0.03	98.11±0.03

Table No. 7: Physical Parameter of Formulations using concentration 160mg of plasticizer

Batch	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug Content (%)
$FPG_{(160)}$	3.0±0.20	0.75±0.13	0.24±0.015	1300±0.03	98.22±0.16
$FG_{(160)}$	3.3±0.32	0.72±0.11	0.29±0.023	1301±0.16	98.55±0.03
$FCA6_{(160)}$	3.2±0.15	0.75±0.12	0.19±0.015	1302±0.12	97.89±0.12

6. *In-vitro* drug release studies

***In-vitro* Dissolution Profile of Formulation of Valsartan Prepared using 120mg concentration of plasticizer by the Direct Compression Method**

The drug release of formulations prepared with PEG400 by direct compression method was performed by a modified dissolution apparatus.

Table No. 8: % Drug release in batches using concentration 120mg of plasticizer

Time	$FPG0_{(80)}$	$FPG1_{(120)}$	$FG3_{(120)}$	$FCA3_{(120)}$
0	0	0	0	0
5	7.578	28.11	37.88	28.94
10	19.33	42.96	38.62	41.12
15	18	53.35	46.17	52.48
20	26.14	64.58	55.66	65.42
25	28.64	76.39	67.13	74.96
30	28.62	89.28	89.63	83.04
35	31.89	92.23	94.88	95.001

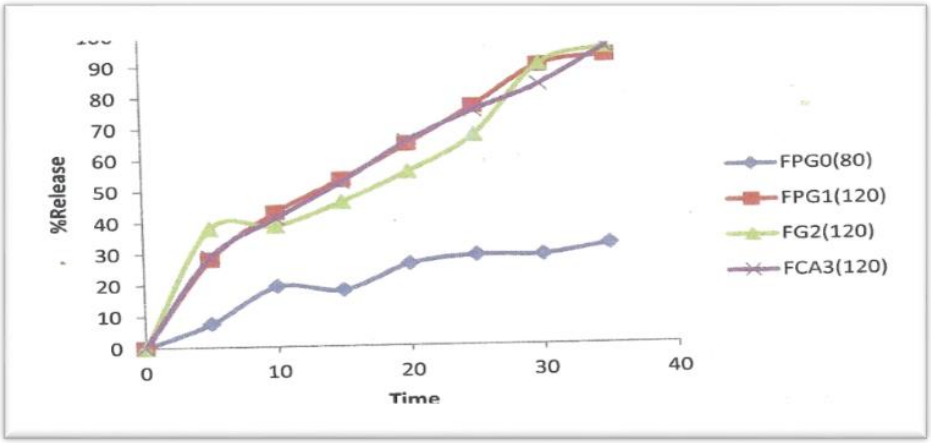

Figure No. 10: Drug release of batches using as plasticizer 120mg

***In-vitro* Dissolution Profile of Formulation of Valsartan Prepared using 160mg concentration of plasticizer by the Direct Compression Method**

Table No. 9: %Drug release in batches using concentration 160mg plasticizer

Time	$FPG0_{(80)}$	$FPG4_{(160)}$	$FG5_{(160)}$	$FCA6_{(160)}$
0	0	0	0	0
5	7.578	27.99	17.82	39.4
10	19.33	44.17	33.68	46.97
15	18	51.43	59.41	50.32
20	26.14	58.54	84.69	77
25	28.64	71.76	92.08	90.23
30	28.62	87.45	91.41	93.41
35	31.89	94.18	101.3	96.77

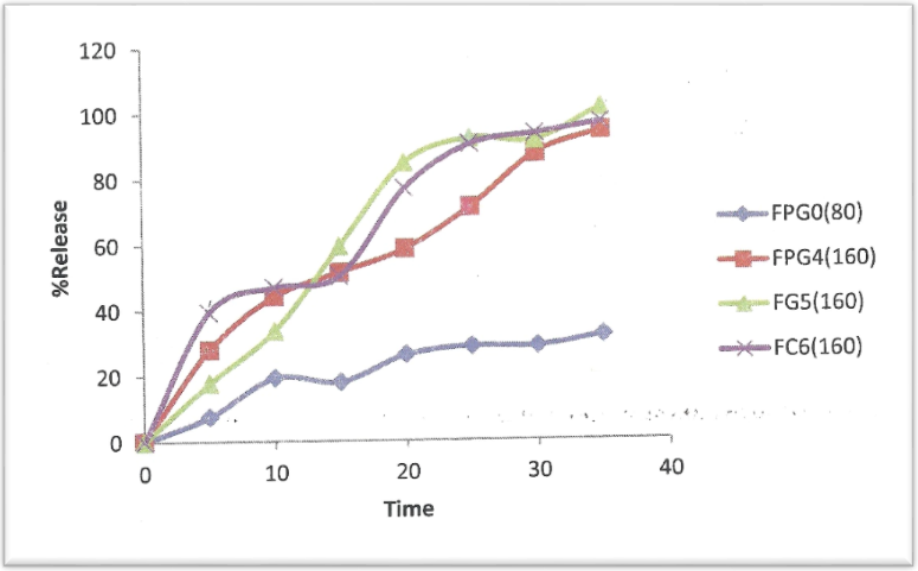

Figure No. 11: Drug release of batches using as a plasticizer 160mg

7. Stability study

The prepared medicated chewing gums were kept at three different temperatures. The first formulation was kept at room temperature, the second formulation was kept in cold temperature and the third formulation was kept in the stability chamber at a temperature of 40ºC/75%RH for 3 months. At the end of 3 months, samples were withdrawn and observed for physical appearance and investigated for % drug release.

Table No. 10: *In-vitro* Drug Release Profile of Stability Batches

Formulation Code	Physical Appearance	Percentage of drug release			
		Initial drug release	Room Temperature (90days)	Cold Temperature (90days)	40ºC/75% RH(90days)
FPG4	No change	94.18%	93.94%	94.12%	94.00%
FG5	No change	101.3%	99.80%	98.85%	98.30%
FCA6	No change	96.77%	96.55%	96.40%	96.00%

CONCLUSION

A medicated chewing gum drug delivery system was developed by using Valsartan as a drug. The medicated chewing gum was prepared by the direct compression method. Medicated chewing gum was evaluated for preformulation study, from the result obtained from the preformulation studies i.e., FTIR and DSC conclude that there was no drug excipient interaction. In the precompression study of blended powder Bulk Density, Tapped Density, percentage Compressibility, Hausner's ration and Angle of Repose was evaluated. We found that all the evaluations result was an acceptable range. After the precompression study medicated chewing gum was formulated by the direct compression method. Prepared formulations were evaluated for hardness, thickness, friability, weight variation, and content uniformity. Reported values suggest that all were found to be within limits. The direct compressed method is much easy, cheaper and shows the highest drug release of 101.3% for the batch FG5 using glycerol as a plasticizer 160mg. It was not changed in physical appearance and drug release after stability study.

REFERENCES

1. Shojaei, A. Buccal Mucosa as A Route for Systemic Drug Delivery: A Review. Pharmaceutical Sciences. 1998;1(1):15-30
2. Bahl, Paul Development of Medicated Chewing Gum Formulation for Formulation for the Delivery of a Poorly Soluble Drug: Doctoral thesis, University of Huddersfield. http://eprints.hud.ac.uk/id/eprint/25435/)2015:21.
3. Christopher A Squire, Mary J. Kremer, Biology of Oral Mucosa and esophagus: JNCI Monographs.2001; 2001(29):7-15.
4. Rebecca Z. German, Jeffrey V. Palmer, Anatomy and Development of Oral Cavity and Pharynx, review, oral cavity, Pharynx and Esophagus GI Motility, 2006.
5. C.A Squier, The Permeability of Oral Mucosa, Critical Reviews in Oral Biology and Medicine. 1991; 2(1):13-32.
6. Chaudary, S. A. & Shahiwala, A. F. Medicated Chewing Gum- A Potential Drug Delivery System. Expert Opinion on Drug Delivery. 2010; 7:871-885.
7. Khatun, S. & Sutradhar, K. B. Medicated chewing gum: An unconventional drug delivery system. International Current Pharmaceutical Journal. 2012; 1:86-91.
8. Biswal, P. K. & Anant Kumar, P. 2013. An updated review on medicated chewing gum International Journal of Advances in Pharmacy, Biology, and Chemistry. 2013; 2:351-359.
9. Abolfazl Aslmi, Farnaz Rostami Medicated chewing gum, a novel drug delivery system: J Res Med Sci. 2015; 20(4):403-11.
10. Kinjal R. Shahl, Tejal A. Metha Medicated Chewing Gum- A Mobile Oral Drug Delivery System International Journal of Pharm Tech Research. 2014; 6(1):35-48.
11. Akbal O, Cevher E, Araman A The development and in vitro evaluation of benzydamine hydrochloride. Medicated chewing gum formulation. Istanbul J Pharm. 2017;47(2):45-51.
12. PoornaTheja, Ashok Kumar, A Review On Medicated Chewing Gums International Journal Of Institutional Pharmacy And Life Science. 2015; 5(1):124-136.
13. Pagare, P. K., Satpute, C. S., Jadhav, V. M. &Kadam, V. Medicated chewing gum: A novel drug delivery system. Journal of Applied Pharmaceutical Sciences. 2012;2(06):40-54.

14. Bales A. Hypertension crisis: How to tell if it's an emergency or urgency. Postgraduate Medicine. 1999; 105(5):119-130.
15. Mohini S Patil 1, Sheetal Z. Godse, Solubility Enhancement ByVarious Techniques: An Overview world Journal Of Pharmacy And Pharmaceutical Sciences. 2013; 2(6)4558-4572
16. Koppula. Rajithal, Yamsani. Madhusudhan Rao Formulation and Evaluation of Medicated Chewing Gums of Chlorpheniramine Maleate International Journal of Pharmacy and Pharmaceutical Research. 2016; 6(2): 73-79.
17. MnasiParadkar, Formulation development and evaluation of medicated chewing gum of anti-emetic drug Saudi Pharmaceutical Journal.2016;24(2):153-164.
18. Tarade Vijay D, Chemate Satyam Z, A Research on Formulation And Evaluation Chewing Gum of Simvastatin. World Journal of Pharmaceutical Research. 2016; 5(4): 1465-1481.
19. PrabhanshuVaishya, Formulation, and evaluation of medicated chewing gum of Ondansetron HCL for chemotherapy-induced nausea and vomiting Scholars Research Library Der Pharmacia Letter.2015;7(5):80-86.
20. Abolfazl Aslani, Alireza Ghannadi, Farnaz Rostami Design, Formulation, and evaluation of ginger medicated chewing gum.2016;5(130):1-9.
21. Sarath Chandran C. Formulation and Evaluation of medicated chewing gums containing methylprednisolone IP International Journal of Chem Tech Research. 2014; 6(11),4810-4816.
22. Abolfazl Aslani et al. Design, formulation and evaluation of nicotine chewing gum. 2012; 1(4):1-5.
23. James N. Rider, Ed L. Brunson Development and Evaluation of Novel Dissolution Apparatus for Medicated Chewing Gum Products. 1992; 9(2): 255-259.
24. Chaudhary, S. A., Shahiwala, A.F., Directly Compressible medicated chewing gum formulation for quick relief from common cold, International Journal of Pharmaceutical Investigated, 2012;2(3): 123-133.
25. AbolfazlAslani et al. Design formulation and evaluation of caffeine chewing gum Published online. 2013; 2(3): 1-6.
26. Nadeem Siddiqui, Asif Husain, Lakshita Chaudhry, M Shamsher Alam, Moloy Mitra and Parminder S. Bhasin Pharmacological and Pharmaceutical Profile of Valsartan: A Review Journal of Appiled Pharmacetical Science. 2011; 01 (04):12-19.
27. Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare 2014; Volume-Ⅲ: 2951-2952.
28. Handbook of Pharmaceutical Excipients fifth Edition by Raymond C Rowe. 2006;5^{th} Edition; Page.No.231, 614, 188, 217.
29. Handbook of Pharmaceutical Excipients fifth edition Edited by Raymond C Rowe. 2006; 5^{th} Edition; Page No 624, 128, 89,449.
30. Subrahmanyam C.V.S, Text Book of Physical Pharmaceutics, second edition, Vallabh Prakashan. 2000; 85.
31. Martin Alfred "Physical Pharmacy'', B. I. Waverly Pvt. Ltd., New Delhi, Fourth edition.1991;760.
32. European Pharmacopeia, Directorate for the Quality of Medicines, Council of Europe, 2010;709.
33. Dr. S. J. Daharwal, Veena Devi Thakur, Shikha Shrivastav and Bhanu Pratap Sahu, Designing and Optimization of Modified Dissolution Apparatus for Evaluation of Medicated Chewing Gum of Ambroxol HCL: Asian Journal of Pharmaceutical Research.2013,3(3):141-143.
34. ICH Q2A, Text on validation of analytical procedures, International Conference on, Harmonization tripartite guidelines, adapted 27 Oct 1994B.