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DEVELOPMENT AND CHARACTERIZATION OF NOVEL ANTIHYPERTENSIVE MEDICATED CHEWING GUM

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ABSTRACT

The objective of study was to design different formulations of medicated chewing gum (MCG) of atenolol HCL and atorvastatin with varying concentrations of softener like glycerol, castor oil and olive oil using conventional method of preparation for buccal administration. Different formulation parameters such as contact time, drug content uniformity, *in vitro* drug release study, and stability properties are studied. MCG 6 showed best contact time (28minutes) and drug content uniformity (94.28%). Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) study confirm the compatibility among drugs and gum base. *In vitro* drug release study and buccal absorption tests shows >70% drug release and >80%buccal absorption within 15 minutes at pH 5.5. Stability studies show no change in physical appearance, sample's color and the softening point of MCG. So MCG of atenolol HCl and atorvastatin can be considered as better formulation for buccal drug delivery system as it avoids first pass effect, provide faster action, and ability to guarantee a fast and complete drug release.

Keywords: Atenolol HCl, Atorvastatin, Castor oil, Glycerol, Medicated chewing gum, Buccal Delivery

INTRODUCTION

Pharmacological active agents can be formulated into a variety of dosage forms like tablets, capsules, syrup, injectables, inhalers, ointments, and creams etc. in which we consider the physicochemical properties and biopharmaceutical parameters of drugs. A Large number of therapeutically active agents are absorbed in the oral cavity and in recent years, scientific and technological advancements have been made in the development of oral drug delivery systems. Oral route has popularity due to its ease of administration. Chewing gum is a convenient drug delivery system which is appropriate for a wide range of pharmacologically active substances and permits more rapid therapeutic action as compared to per-oral dosage forms **[1]**.

MCG are defined by the European Pharmacopoeia and guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use as ‘‘solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed, providing a slow steady release of the medicine contained”. MCG are solid single dosage form of a masticatory gum core with a coating of film of polymers, waxes, flavors or colors having therapeutically active ingredients in the core, in the coating or in both. MCG is currently available for smoking cessation, pain relief, motion sickness and freshening of breath **[2]**.

Drug candidates selected as a MCG should have physicochemical Properties like high salivary solubility, pH independent solubility, tasteless, not affecting salivary flow rate and patient related factors include; should be non-toxic to oromucosa and salivary ducts, non-carcinogenic and should not cause tooth decay **[3]**.

Release rate of active medicament from a chewing gum is determined by physico-chemical properties of drug, composition and manufacturing process of formulation and by patient chewing performances (Jacobsen J et al., 2004). Patient chewing performance means people show different chewing time, chewing frequency, chewing intensity and moreover patients with xerostomia or oromucosal diseases may experience different chewing performances **[4, 5]**.

Quantity of drug delivered by medicated chewing gum will depend on mechanical chewing action, chewing force, and chewing intensity. Particle size of drug should be kept

below approximately 100 µm to avoid unpleasant gritty feeling during chewing.

During process of chewing, drug present in the gum is released from product into saliva & absorbed through oral mucosa or swallowed and reaching into stomach for gastro-intestinal absorption **[6]**.

The objective of present work was to develop and characterize medicated sugar free chewing gum delivery of atenolol HCl and atorvastatin for the treatment of hypertension and hypercholesterolemia and evaluate the important formulation parameters of MCG.

MATERIALS AND METHODS

Materials

Atenolol HCl, atorvastatin and orange flavor were gifted by high noon laboratory (Lahore, Pakistan Ltd). Gum base of food grade was gifted by gumcorp industry (Karachi, Pakistan Ltd). Fine dry powder of glycerrhiza, paraffin wax, glycerin, olive oil and castor oil of food grade were purchased from Ali Baba (food grade products and chemical supplier company, Lahore, Pakistan Ltd). Green color of food grade was purchased from market. Most of the chemicals used in research were of analytical grade.

Method

MCG was prepared by the traditional method (Athanikar NK, 2001**)**. Total nine formulations were prepared in this study with different combinations of softeners like formulations MCG 1, 2, 3 made with glycerin, formulations MCG 4, 5, 6 made with castor oil and formulations MCG 7, 8, 9 made with olive oil (Table 1). First, synthetic gum base and paraffin wax was melted in porcelain dish at about 35-45 ºC on steam bath. Secondly, previously weighed quantity of softeners like glycerin, castor oil and olive oil for each formulation were added to this molten mass and then mixed thoroughly. Mixture was allowed to cool at temperature of 15-20 ºC and then added physically homogenous mixture of atenolol HCl, atorvastatin, talc (as anti-adherent) and glycerrhiza (as a sweetener) with continuous stirring to ensure even distribution of drugs. At the end, orange flavor and color were added. Then this gum mass was allow to cool at carefully controlled room temperature for up to 48 hours on steel plate, so that gum mass is set properly and then this gum mass was rolled evenly and finally cut gum mass into pieces of required uniform size and weighed pieces were removed and wrapped properly and cooled carefully under the carefully controlled temperature and

humidity. Each chewing gum was made with net weight of 2g **(Table 1)**.

Table 1: Different formulations and their ratios of ingredients, (weight in mg)

Sr. No.	Ingredients	MCG-1	MCG-2	MCG-3	MCG-4	MCG-5	MCG-6	MCG-7	MCG-8	MCG-9
1	Atenolol HCl	25	25	25	25	25	25	25	25	25
2	Atorvastatin	10	10	10	10	10	10	10	10	10
3	Gum base	500	500	500	500	500	500	500	500	500
4	Glycerin	100	200	300	---	---	---	---	---	---
5	Castor oil	---	---	---	100	200	300	---	---	---
6	Olive oil	---	---	---	---	---	---	100	200	300
7	Paraffin wax	100	100	100	100	100	100	100	100	100
8	Talc	100	100	100	100	100	100	100	100	100
9	Glycerrhiza	1045	945	845	1045	945	845	1045	945	845
10	Flavoring agent	100	100	100	100	100	100	100	100	100
11	Color agent	20	20	20	20	20	20	20	20	20

CHARACTERIZATION OF MEDICATED CHEWING GUM

Contact time

MCG contact time is responsible for local or systemic effect in oral cavity. Ordinary chewing time was considered 30 minute in clinical trial **[23]**. Four healthy volunteers were selected for this study. Each person was allowed to chew one piece of MCG as long as they could, so that its maximum contact remain in the oral cavity and when volunteer expel MCG from mouth, that time was observed and reported.

Physical evaluation

All formulations were physically evaluated for Appearance, Color, Hardness, Stickiness, Plasticity, Weight variation and Drug Content **[7, 8]**.

Hardness/Plasticity

Hardness / Plasticity of all MCG formulations was determined by Monsanto Type Hardness Tester due to absence of any reported method for the determination of hardness/plasticity **[7, 8]**.

Weight variation

Weight variation of all formulation was done by method described in the experimental work **[7, 8]**. Ten chewing gums were taken randomly. Unit weight of each chewing gum and average weight was calculated, and then standard deviation was determined.

Stickiness

The MCG was placed on the plain surface, Teflon hammer (250 gm) collide on it for period of ten minute at a frequency of about 30 / minute. Any stickness of mass to hammer surface was observed and reported after 10 minutes **[7, 8]**.

Stability study of medicated chewing gum

For the purpose of stability study, 10 pieces of MCG was stored in bottle at temperature of 30 ± 02 ºC and relative humidity (RH) of 65 ± 5% for the period of six months. After six months, MCG was examined for natural ageing and physical nature.

Stability study of gum base

In stability studies, 10 gram of synthetic gum base was stored in bottle at temperature of 30±02 ºC and relative humidity of 65% ± 5% (According to WHO guideline for stability studies) for the period of six months. After six months gum base was examined for natural ageing and physical nature **[7]**.

Fourier Transform Infrared Spectroscopy (FTIR)

Drugs and synthetic gum base interactions were observed by using FTIR Prestage 21 (Shimadzu Japan). Sample preparation was done in KBr disks (2 mg sample in 200 mg KBr). The scanning range, resolution and hydraulic pressure was kept 400–4000 cm^{-1}, 2 cm^{-1} and 150 kg/cm^2 respectively. IR spectra were recorded for pure drugs (atenolol HCl and atorvastatin), pure synthetic gum base, combination of drugs (atenolol HCl and atorvastatin), and combination of drugs and synthetic gum base (atenolol HCl, atorvastatin and synthetic gum base) **[9]**.

Differential Scanning Calorimetry (DSC)

DSC analysis of pure drugs (atenolol HCl and atorvastatin), synthetic gum base and drug- synthetic gum base was conducted on SDT by Q600 TA USA for evaluating any possible drug- synthetic gum base combination.

Drug, synthetic gum base and their combinations were triturated to make them fine in size and heated in sealed Aluminium pan at a heating rate of 10 ºC/min from 0 to 226 ºC by keeping nitrogen flow of 40 ml/min. Reproducibility was checked by running sample in triplicate **[9]**.

***In vitro* drug release**

Apparatus I. Chewing Gum Apparatus, Compendial-Ph. Eur.

Chewing apparatus comprised of a chewing chamber, two horizontal pistons, and a vertical piston (tongue). Vertical piston operates alternatively with two horizontal pistons to makes sure that gum stays on right place between chews. If necessary, it is feasible to construct machine so that at the end of chew horizontal pistons rotate around their own axis in opposite directions to obtain maximum chewing.

Chewing procedure for *in vitro* drug release based on **[10, 11, 12]**;

1) Change in the twisting angle of upper mastication jaw from 5-30 ºC.
2) Change in distance b/w upper and lower masticating jaw from 1-2 mm.

3) Change in frequency of lower masticating jaw from 20 strokes per minute to 120 strokes per minute.
4) Change in temperature from 30-40 ºC.

Chewing procedure consist of up and down stroke of lower masticating surface with twisting movement of upper masticating surface for masticating chewing gum that was placed between the pistons on to lower chewing surface at optimized chewing frequency of 60±2 strokes per minute while being agitating test medium. Aliquot of artificial saliva were removed at predetermined time interval and analyzed by using UV spectrophotometer for drug content. After taking each sample, release medium was replaced with fresh artificial saliva **[13, 14, 15]**.

Modified release study on healthy volunteer

Human ethical committee approval letter from university

All information regarding study of MCG including buccal absorption test, release of drug in saliva, dissolution test of residual MCG, urinary excretion profile of MCG on healthy volunteers were provided to the human ethics committee of the faculty of pharmacy, university of Sargodha. Human ethics committee head and all members analyzed this study in relation to human safety, ethical principles, clinical outcome and give permission to carryout study. Approval was given for a period of twelve month and when study completed, he submit the final study report to the department ethics committee. Member of committee checked study process time to time and found research in accordance with guidelines established by the university and he informed about any alteration made during study to the committee before its approval.

It is ensured that all research conducted by researcher's is conform to the university ethical principles and safety procedures and is related to clinical outcomes.

Buccal absorption test

It was done by introducing each drug solution (25 ml) with different concentration; for atenolol HCl (0.5 mg / ml) and for atorvastatin (0.4 mg / ml) at different pH value of 1.2, 4.5, 5, 6, 6.5, 7, 7.5, 7.8, 8, in the oral cavity of human volunteer who swirled it for 15 min and then expelled out. The expelled saliva was analyzed of atenolol HCl at 276 nm and of atorvastatin at 247nm by UV spectrophotometric method against blank reagent **[16]**.

Release of drug in saliva

In this method, all formulations of medicated chewing gum with good consistency were

selected for the release of drugs in saliva. Four human volunteers were selected (two male and two female), instructed to rinse their mouth with distilled water and allowed to chew the medicated chewing gum for 15 minutes. Sample of saliva was taken after 5 minutes and then at intervals of 2, 4, 6, 8, 10, 12, 14, 15 min. The saliva sample was made diluted in the phosphate buffer (pH 6.8) and absorbance was analyzed for atenolol HCl at 276 nm and for atorvastatin at 247 nm by UV spectrophotometric method against blank reagent **[17]**.

Dissolution test of residual medicated chewing gum

In current experiment, a panel of volunteers tested Gums to verify drug release process from drug delivery system. One sample of gum was chewed for different time periods (1, 5, 10, 15 min) by each person. Residual gums had been cut into small pieces, frozen and then ground till a fine powder. The residual drug content had been determined by UV spectrophotometer using dissolution test apparatus (U.S.P. dissolution test apparatus, 100 rpm and at 37°C). The amount of drug released during mastication is calculated by subtracting the amount of residual active ingredient present in gum from total content **[18]**.

Urinary excretion profile of medicated chewing gum

Four healthy human volunteers were selected. They were strictly instructed not to take any medicine in the last 48 hours and emptied their bladder in volumetric flask. Sample collection started after administration of medicated chewing gum at 0, 15 min, and 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hours interval. Volunteers were asked to drink water at regular intervals of 30 min. and absorbance was analyzed by UV spectrophotometer for atenolol HCl at 276 nm and for atorvastatin at 247 nm against blank reagent **[19]**.

RESULTS & DISCUSSION

Physical evaluation

All formulations were physically evaluated for Appearance, Color, Hardness/ Plasticity and Stickiness. These all were found within the limit of normal range **(Table 2).**

Table 2: Physical characteristics of formulations

Formulations	Color	Appearance	Stickiness	Pressure required to press gum (kg/cm2)
MCG1	Dark green	Hard	Nil	2.4
MCG2	Green	Hard	Nil	2.8
MCG3	Light Green	Soft	Nil	1.9
MCG4	Green	Hard	Nil	2.5
MCG5	Dark green	Soft	Negligible	1.5

MCG6	**Light Green**	**Soft**	**Negligible**	**1.7**
MCG7	**Green**	**Soft**	**Nil**	**1.8**
MCG8	**Dark green**	**Soft**	**Nil**	**2.1**
MCG9	**Light Green**	**Hard**	**Negligible**	**2.5**

Contact time

From above study, contact time of MCG in oral cavity was found average 26 min, which was considered in normal limit and best contact time of MCG 6 with castor oil softener was found 28 minute in oral cavity because castor oil don't stick with tongue or teeth so provide smooth mastication.

Melting point

The melting point of atenolol HCl and atorvastatin was found to be 154 ℃ and 176 °C respectively while standard values were found to be in the range of 152-155 °C and 176-178 °C. It means drugs used were pure ones.

Identification test

The λ_{max} for atenolol HCl and atorvastatin was found to be 276 nm and 247 nm in medium of phosphate buffer having pH 6.8 respectively.

Weight variation

Average weight of ten medicated chewing gums was found to be 1.98 g while net weight of each chewing gum was 2 g and it was within normal range.

Stickiness

Stickiness of all formulations was found negligible (Table 3) that improves patient's compliance and confidence because drugs release from MCG very smoothly.

Softening property of gum base

Softening range of synthetic gum base was suitable for formulation of medicated chewing gum.

Softening property of medicated chewing gum

Softening property of MCG was remained suitable during storage conditions of its shelf life that improves patient's compliance and confidence.

Moisture absorbance study of gum base and MCG

Synthetic gum base and MCG remain stable during their shelf lives and both absorbed very less percentage of moisture during storage period.

Solubility studies of gum base

Gum base was found best candidate as chewing gum base for formulation of MCGs because sample of gum base shows less than 1%, 1.92% and 1.921% solubility in alcohol, diethyl ether and in chloroform respectively. Solubility of gum base in phosphate buffer was found almost negligible, so gum base

confirms its insoluble nature and gain importance for use in MCGs formulations.

In vitro drug release

It was found that drug release from all formulations after 15 minute was more than 70%. These findings show longer oral presence of MCG in the oral cavity and graph shows comparative drug release study of all formulations in 30 minutes. It was found that formulation MCG 6 shows better release than other formulations. So it was concluded that formulation MCG 6 was selected as a best batch and carried out further for his stability study. Optimized setting for twisting angle was 20º as twisting angle movement for upper masticating jaw, 99% drug release was noted after 29 minute, which shows that rate of drug release increased significantly by increasing twisting angle. Chewing frequency of the lower masticating jaw is important factor in the masticating process because drug release profile shows significant increase by increasing frequency of chewing or movement of lower masticating jaw.

For all formulations increase in the rate of drug release as we decrease the distance between upper and lower masticating surface from 2 mm to 1 mm since the force acting on gum is larger than 1 mm setting. High kneading speed between the jaws of chewing apparatus leads to increase in the release rate of drug and decrease in time interval for release. There was no significant effect on drug release profile for all formulations as we increase the temperature from 30-40 ºC.

Effectiveness of formulation MCG 6 was also analyzed by statistical analysis using ANOVA where castor oil, glycerin and olive oil was used for each of the above described parameters in which results were confirmed by defining p value where if p value is less than 0.05 then results are significant means formulation is not according to expectations and if p value is greater than 0.05 then results are insignificant means formulation is according to expectations. Values for parameters using castor oil, glycerin and olive oil were 0.827, 0.695 and 0.804 which are greater than 0.05 so our results were insignificant, means our formulation is according to expectations and formulation MCG 6 is best formulation containing castor oil as shown by the p value. **(Table 3, 4, 5 and Figure 1)**.

Stability study

Stability study of MCG show that there was no change in physical appearance, color of stored samples and the softening point of

gum which confirms the stability study of MCG **(Table 6)**.

Table 3: *In vitro* drug release with chewing frequency setting of 60 strokes/minute

Time interval (min.)	Cumulative % drug release (formulations codes)								
	MCG-1	MCG-2	MCG-3	MCG-4	MCG-5	MCG-6	MCG-7	MCG-8	MCG-9
0	0	0	0	0	0	0	0	0	0
5	31	33	33	32	32	34	30	32	29
10	54	53	54	52	52	56	51	53	50
15	73	74	74	73	74	76	70	72	71
20	82	83	84	83	84	86	80	83	80
25	89	90	91	90	92	94	88	91	87
30	93	95	96	95	97	99	94	96	92

Table 4: *In vitro* drug release with distance setting between the jaws 1.5 mm

Time interval (min.)	Cumulative % drug release (formulations codes)								
	MCG-1	MCG-2	MCG-3	MCG-4	MCG-5	MCG-6	MCG-7	MCG-8	MCG-9
0	0	0	0	0	0	0	0	0	0
5	30	32	32	31	32	34	30	32	28
10	52	53	54	51	53	55	51	53	49
15	72	72	74	71	73	74	70	73	68
20	82	83	83	82	82	84	81	82	78
25	89	91	91	90	90	92	89	90	86
30	93	95	96	95	96	98	94	96	92

Table 5: *In vitro* drug release with setting of twisting angle at 5°

Time interval (min.)	Cumulative % drug release (formulations codes)								
	MCG-1	MCG-2	MCG-3	MCG-4	MCG-5	MCG-6	MCG-7	MCG-8	MCG-9
0	0	0	0	0	0	0	0	0	0
5	27	28	30	29	30	31	28	30	27
10	46	48	50	50	51	53	49	51	48
15	61	63	65	66	66	69	63	67	62
20	70	72	74	74	76	78	72	75	70
25	78	79	81	80	82	84	79	81	77
30	84	84	86	85	87	90	83	86	81

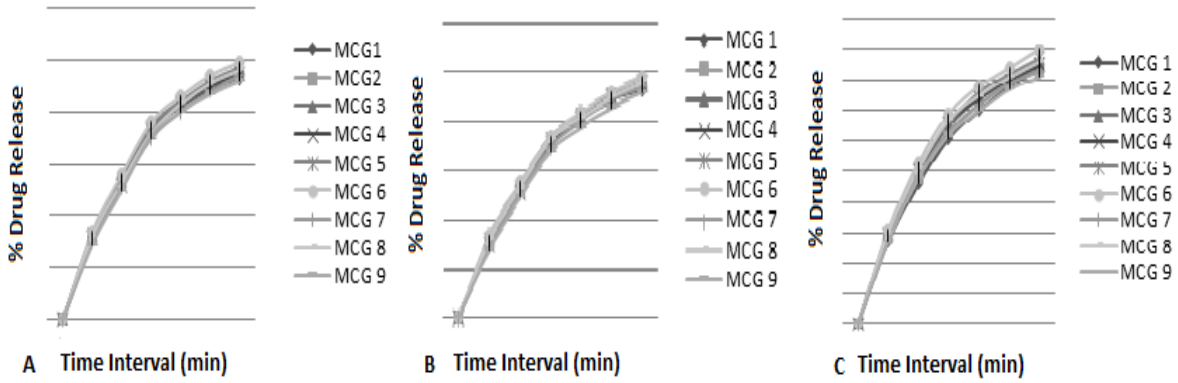

Figure 1: *In vitro* drug release with A: chewing frequency setting of 60 stroke/min, B: distance setting between the jaws 1.5 mm, C: setting of twisting angle at 5°C.

Table 6: Physiochemical properties of synthetic gum base after stability Studies

Sr. No.	Properties	Observations
1	Color (before aging)	Off white-light yellow
2	Color (after aging)	Off white-light yellow
3	Softening range (before aging)	87-92 °C
4	Softening range (after aging)	87-92 °C
5	Texture (before aging)	Gummy
6	Texture (after aging)	Gummy

Drug content uniformity

It was found between ranges of 91% to 97% and average value was found 94.28 that are within the normal range. Formulations were found having uniformity in the contents of the drug as atenolol HCl (25mg) and atorvastatin (10 mg) in all formulations **(Table 7)**.

Table 7: Contents uniformity of various formulations

Formulations	% Purity
MCG1	92.65
MCG2	92.55
MCG3	94.87
MCG4	96.00
MCG5	96.26
MCG6	97.75
MCG7	92.25
MCG8	94.35
MCG9	91.88

Modified release study on healthy volunteers

These results proved that medicated chewing gum as dosage form was a good administration system. Drug release from the dosage form is the critical step in drug absorption and its bioavailability so simple diffusion into medium caused release of only small percentage of drug contained in medicated chewing gum, while delivery of major part of dose occur during mastication. According to therapeutic requirements it was confirmed that MCG provide rapid and complete drug release after a relatively brief chewing time. The total amount, contained in the MCG dosage form, is delivered after lowest mastication time (1 min) and there is no significant increase of drug recovery from gum cuds as detected by increasing mastication time.

As the comparison point of view the gum formulations contained castor oil as plasticizers provide better dosage against glycerol and olive oil combinations.

From modified release study on healthy volunteers, better consistency of formulation and faster release of drug in saliva was obtained with glycerol MCG 3, castor oil MCG 6 and olive oil MCG 8 but castor oil shows optimum results against others softeners combinations, which is MCG 6. It was found that 15 minute chewing of atenolol HCl and atorvastatin MCG more than 80% of drug absorbed in buccal cavity

at pH 5.5, which can be considered the mean chewing time of a gum.

So therapeutic product is readily available for absorption because there is no significant difference can be observed among this quantity that is obtained after 10-15 minute chewing.

Formulations containing castor oil as a plasticizer, released almost all of the actives in a very short mastication time (11 min.) because different behavior could be explained by considering the varying concentration of active principles and plasticizers. So drug release rate seems to be dependent upon water solubility and nature and concentration of plasticizer.

Urinary excretion data showed that Drugs were excreted by passing the first pass effect of drug within short period of time (2 hours). Buccal absorption test showed that more than 80% of drug absorbed within 15 min when available to the buccal mucosa at pH 5.5 **(Table 8)**. So medicated chewing gum of atenolol HCl and atorvastatin can be considered as better, faster and novel formulation for buccal drug delivery system so as to avoid first pass effect, reduce risk of over dosing, easy administration and faster action.

Table 8: Buccal absorption test at different pH of formulation MCG6 containing castor oil

pH of buffer solution (MCG6)	% drug absorbed
5	68.50±o.15
5.5	82.13±0.12
6	74.33±0.60
6.5	70.45±0.56
7	63.45±0.35
7.5	57.25±0.33
8	52.60±0.18

Fourier Transform Infrared Spectroscopy (FTIR) Results

The FTIR spectra of atenolol and atorvastatin alone and in combination with synthetic gum base was taken. The FT-IR spectra of pure atorvastatin calcium showed characteristic peaks at 2955.15 cm^{-1} (C-N - stretching), 3059.15 cm^{-1}(C-H - stretching), 1313.56 cm^{-1}(C-HO - stretching alcoholic group), 1564.97 cm^{-1} (C=O - stretching amidic group), 3403.27 cm^{-1} (N-H - stretching), 1656.97 cm^{-1} (C=C - bending), 751.62 cm^{-1}, 696.95 cm^{-1} (C-F - stretching), 1104.39 cm^{-1} (O-H - bending).

It might be possibility of intermolecular hydrogen bonding between adjacent atorvastatin calcium molecules. The spectrum of pure atorvastatin calcium was equivalent to the spectra obtained by the addition of synthetic gum base **[20]**.

IR spectrum of atenolol is characterized by the absorption of -COOH group at 1651 cm^{-1}.

Same absorption spectrum of atenolol was obtained**.** The results revealed no considerable changes in IR peaks of atorvastatin calcium, when mixed with drug atenolol and with synthetic gum base.

These observations indicated the compatibility of atorvastatin calcium and atenolol with each other as well as compatibility of atorvastatin calcium and atenolol with synthetic gum base **(Figure 4) [21]**.

Differential Scanning Calorimetry (DSC) Results

DSC studies were conducted to check any incompatibility among drugs and excipients. The whole study was conducted on SDT. Q600 Thermal Analyzer USA at increasing temperature rate of 10 ºC/min for a specific time period for a particular agent.

In case of individual drugs (atenolol HCl and atorvastatin) initially, flat or smooth profile was observed but when it entered in to its melting range 154 ^{o}C and 176^{o}C respectively, sharp exothermic peaks were observed.

DSC thermograms of these drugs (atenolol HCl and atorvastatin) were also taken with synthetic gum base. The comparison of characteristic thermograms of alone drugs and with synthetic gum base and data scanned have not exhibited any change when drugs were tested alone or in combination, even there was no shift of peaks while drugs were in combination.

This study confirmed no interaction among atenolol HCl, atorvastatin and synthetic gum base when used alone or formulated in combination **(Figure 5) [22]**.

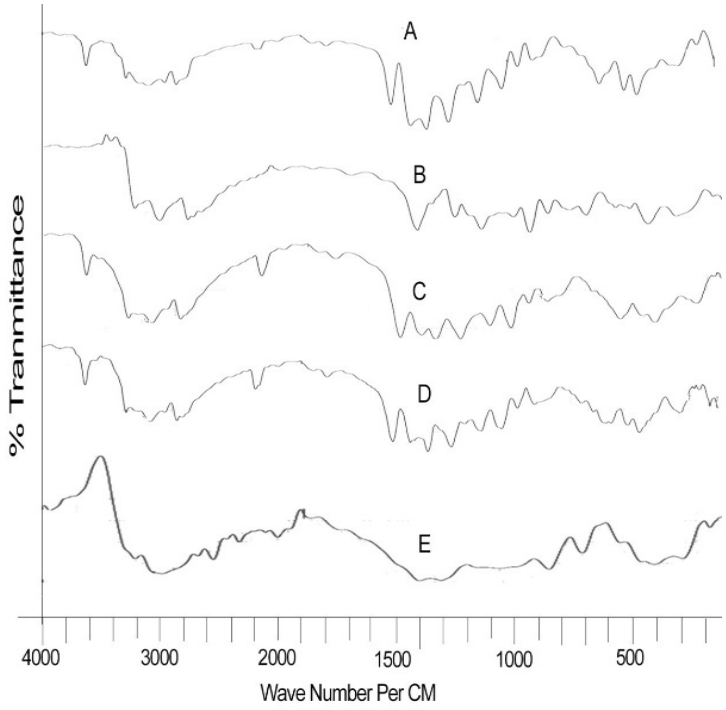

Figure 4: FTIR spectrum of Atorvastatin, Atenolol HCl, Gum base alone and combined. A: Atorvastatin, B: Atenolol HCl, C: Atorvastatin + Atenolol HCl, D: Atorvastatin + Atenolol HCl + Gum base, E: Gum base

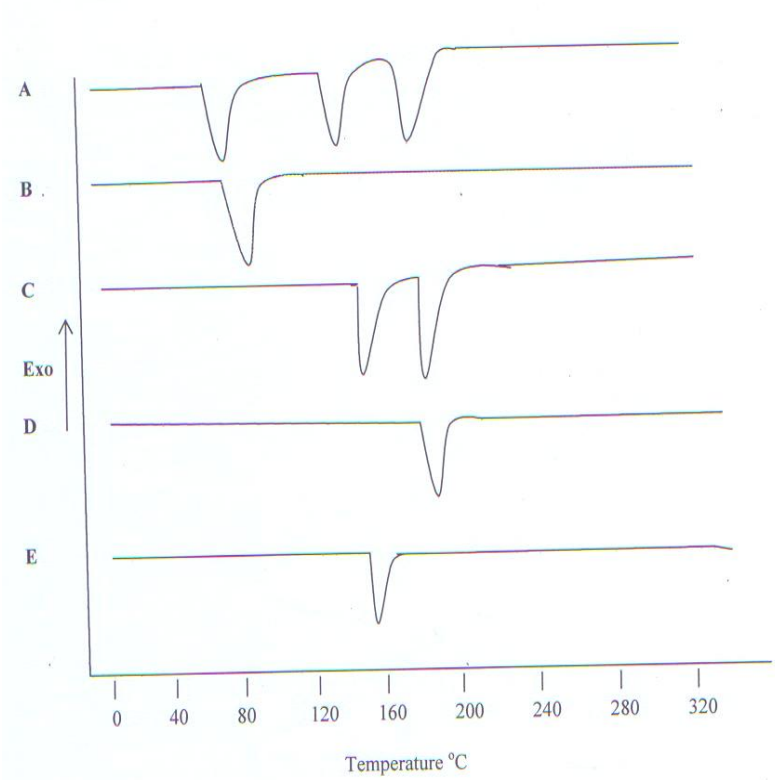

Figure 5: DSC results of Atenolol, Atorvastatin, Gum base alone and in combination. A Atenolol + Atorvastatin + Gum Base, B- Gum Base, C- Atenolol + Atorvastatin, D- Atorvastatin, E- Atenolol

CONCLUSION

Results of stability study, *in vitro* release profile and use of gum base in the concentration of about 25% found high steady release of drug from formulation MCG 6 (content uniformity 97.75%). The dissolution curves showed a satisfactory release rate. Gum base used (concentration 25%) to formulate MCG provide a more pleasant mouth feel and steady and controlled release of drug as compared to marketed MCG. The FTIR spectrum showed the compatibility of Atorvastatin Calcium and Atenolol with each other as well as with synthetic gum base.

The DSC confirmed no interaction among Atenolol HCl, Atorvastatin and synthetic gum base when used alone or formulated in combination. MCG can be considered a better formulation for buccal drug delivery as it avoids first pass effect, provide faster action, and ability to guarantee a fast and complete drug release.

FUTURE TRENT OF MEDICATED CHEWING GUM

Cheaper medicines are continuous demand from health sector and it is true that cheaper medicines are needed to reduce treatment cost with efficacy and safety. In this sense, novel drug delivery technologies will continue to be developed and providing innovation for the end users and market differentiation for the pharmaceutical companies. In the coming year it is very likely that more research will be done on medicated chewing gums and it's becoming a common drug delivery system.

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