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Formulation and evaluation of mucoadhesive buccal tablets of losartan by using natural polymers.

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ABSTRACT

Losartan, a drug widely used in the treatment of hypertension. However, its extensive first pass metabolism results in poor bioavailability. The objective of present research work is to design and evaluate the sustained release of mucoadhesive buccal tablets of Losartan with a goal to increase the bioavailability, reduce dosing frequency and improve patient compliance. The tablets were prepared using Gum Kondagagu, Gum Olibanum and Guar Gum as mucoadhesive polymers. Nine formulations were developed with varying concentration of polymers. The tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, Surface pH, *in-vitro* studies like swelling, mucoadhesive strength and drug release. Formulation (F6) containing Gum Olibanum with highest concentration showed good mucoadhesive strength (24.43) and maximum drug release of 99.15% in 6 hrs. Swelling increase with increase in concentration of Gum Olibanum in tablets. Swelling pH was found to be 6.10. Formulation (F6) follows zero-order drug release. FTIR studied showed no evidence on interaction between drug and polymers. The results indicate that the mucoadhesive buccal tablets of Losartan may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Losartan through buccal mucosa.

Keywords: Losartan, Mucoadhesive, Swelling Index, Gum Kondagagu, Gum Olibanum.

INTRODUCTION

Mucoadhesive drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers. Bioadhesion is defined as an ability of a material to adhere a particular region of the body for extended period of time not only for local targeting of drugs but also for better control of systemic delivery. Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, rapid termination of therapy and administration to unconscious patients. Drug which are destroyed by the enzymatic/alkaline environment of the intestines are unstable in the acidic environment of the stomach can be administered by this route[1].

Most of the mucoadhesive materials are either synthetic or natural hydrophilic or water insoluble polymers and are capable of forming numerous

hydrogen bonds because of presence of the carboxyl, sulphate or hydroxyl functional groups. Various materials were tested for mucoadhesion. The natural polymers include xantium gum, sodium alginate, Gum Kondagagu, Gum Olibanum, gelatin, acacia and tragacanth[3]**.** The bioadhesive polymers can not only cause the adhesion effects but can also control the release rate of drug.

Losartan is a selective, competitive angiotensin II receptor type 1 (AT1) antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (after load) and cardiac venous return (preload). All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. The objective of present study is to formulate and evaluate the of mucoadhesive buccal tablets of Losartan with a goal to increase the bioavailability, reduce dosing frequency and improve patient compliance. The buccal tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, surface pH, *in-vitro* studies like swelling, mucoadhesive strength and drug release[4]**.**

MATERIALS AND METHODS

Materials

Losartan was received as gift sample from ***Alembic Ltd.,*** Vadodara, and Gujarat. Gum Kondagagu, Gum Olibanum and Guar Gum were procured as gift samples from Girijan society. Hyderabad, India. All other reagents and chemical used of analytical grade.

Preparation of mucoadhesive buccal tablets[5]

Mucoadhesive buccal tablets, each containing 50 mg Losartan were prepared by direct compression method. Compositions of various formulations employing Carbopol 934P, HPMC K4M & HEC are shown in Table 1. All the ingredients of tablets were blended in mortar with a pestle for 15 min to obtain uniform mixture. The blended powder was then compressed into 150 mg tablets (at 4-6 kg/cm^2) on a single stoke, 10 station rotary tablet machine (***Cadmach*** Machinery Co. Pvt. Ltd., ***Ahmedabad***, india) with 8mm round shaped flat punch.

Table 1: Composition of Mucodhesive Buccal Tablets

S.No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Losartan**	50	50	50	50	50	50	50	50	50
2	**Gum Kondagagu**	5	10	15	-	-	-	-	-	-
3	**Gum Olibanum**	-	-	-	5	10	15	–	–	-
4	**Guar Gum**	–	–	–	–	-	-	10	20	30
5	**Lactose**	85	80	75	85	80	75	80	70	60
6	**Mg stearate**	2	2	2	2	2	2	2	2	2
7	**Talc**	2	2	2	2	2	2	2	2	2
8	**PVP K30**	6	6	6	6	6	6	6	6	6
	Total wt (mg)	150	150	150	150	150	150	150	150	150

Evaluation of tablets

The tablets from different formulation (F1 to F9) were subjected to followed tests:

Hardness

Tablets were evaluated for their hardness using Monsanto hardness tester.

Weight Variation

Ten tablets from each formulation were weighed using an electronic digital balance and the average weight was calculated. The results are shown in **Table-2.**

Thickness

Tablets were evaluated for their thickness using slide calipers. The results are shown in **Table 2.**

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 10 mg of Losartan equivalent of mixture was extracted thoroughly with 100 ml of methanol. The amount of drug present in extract was determined using UV Spectrometer at 284 nm. The results presented in **Table 2.**

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any *in vivo* side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa. The method developed by Battenberg *et al* was used.

A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min. The results are shown in **Table 3**.

In vitro swelling studies[6]

The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive. For conducting the study, a tablet was weighed and placed in a petri-dish containing 5 ml of phosphate buffer at pH 6.8 for 12 hrs, the tablets were taken out from the petri-dish and excess water was removed carefully by using filter paper. The swelling Index was calculated using the following formula and results are summarized in Table 3.

Swelling Index (SI) + (Wt-Wo)/Wo X 100

Where SI= Swelling index.

Wt = Weight of tablets after time at 't'.

Wo = Weight of tablet before placing in the beaker.

In vitro drug release profile[9]

The United States of Pharmacopoeia (USP) XXIV rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, with rotation speed of 50 rpm. Samples (5ml) were withdrawn at predetermined time intervals (1, 2, and 3…6 hrs) and volume was replaced with the fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at 284 nm. The experiments for different formulations (F1 to F9) were conducted in triplicate and average values were recorded and found the release kinetics such as zero order, first order, Higuche and Hixconcrowell were determined & the data are shown in Table 3.

RESULTS AND DISCUSSION

Total Nine different formulations (F1 to F9) of Losartan buccal tablets were prepared by direct compression techniques using various proportions of polymers and excipients. In order to select the best formulations, various evaluation parameters were checked and subjected to *in-vitro* dissolution studies and their release profiles.

Hardness

The hardness of tablets of different formulation (F1 to F9) was determined as per standard procedure. The average hardness of tablets was found to be 3 to 4 kg/cm. None of the formulations showed deviation for any of the tablets tested

Thickness of Tablets

The average thickness of tablets (F1 to F9) determined and results are presented in Table 2. The maximum and minimum average thickness of tablet was found to 3 mm and 2.5 mm respectively. None of the formulation (F1 to F9) deviated from the standards.

Content uniformity

The content uniformity of the entire tablet (F1 to F9) was evaluated and the results are presented in Table 3. The maximum percentage of drug content from the different formulations was found to be 99.82 and minimum percentage of drug content was found to be 99.12 %. Hence it is concluded that all the formulations are falling within the pharmacopoeial limits.

Surface pH

The surface pH of tablets of each formulation (F1 to F9) was tested and the results are provided in table-3. The maximum and minimum pH values

of the formulations were found to be 6.10 and 5.59 respectively. The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets is within limits. Hence, the formulations may not produce any irritation to the buccal mucosa.

In vitro drug release profile

The drug release pattern was studied for all formulations (F1 to F9) for 6 hrs following standard procedure and the results are provided in Fig. 5. The drug release pattern of buccal mucoadhesive tablets varied according to their type and ratio of polymers. The in vitro cumulative drug release profile of formulations F1, F2, F3 at 6 hrs showed 80.7 %, 81.05 % and 86.15 % drug release respectively.

Similarly the formulations F4, F5, F6, F7, F8 and F9 at 6 hrs showed81.95 %, 92.15 %, 99.15 % and 78.00 %, 84.05 % and 87.55 % drug release respectively. This may be attributed to increased hydration followed by increased swelling of polymers with increase in concentration.

The overall data on the *in vitro* dissolution studies closely indicated that among the six formulations, the formulation F6 was found to be the best with high percentage of drug release (99.15). The cumulative drug release of formulations was found to be in order of **F6>F5>F9>F3>F8>F4>F2>F1>F7.**

Table 2: Post Compression Evaluation Tests of Tablets

FORMULATION	Weight variation (mg)	Thickness (mm)	Hardness Test (Kg/cm^2)	Friability (%)	Drug content (%)	Surface pH
F1	149.0±2.0	2.17±0.04	3.33±0.05	0.61±0.01	97.53±0.31	6.01 ±0.22
F2	148.5±1.8	2.15±0.03	3.43±0.05	0.65±0.03	99.62±0.15	6.43±0.27
F3	150.0±1.2	2.20±0.05	4.43±0.11	0.68±0.06	99.56±0.22	6.17 ±0.20
F4	149.0±1.9	2.17±0.01	3.83±0.05	0.69±0.07	99.49±0.3	6.18 ±0.33
F5	150.5±1.2	2.15±0.03	3.53±0.05	0.72±0.05	99.75±0.11	6.57 ±0.19
F6	150.0±1.7	2.25±0.04	3.56±0.05	0.63±0.04	99.82±0.11	6.19 ±0.30
F7	148.5±1.3	2.17±0.04	3.03±0.05	0.74±0.02	98.51±0.04	6.29 ±0.30
F8	149.7±1.5	2.30±0.03	4.73±0.05	0.77±0.02	99.12±0.11	6.91 ±0.49
F9	148.5±1.8	2.15±0.03	4.33±0.05	0.65±0.03	99.62±0.15	6.33±0.27

Table 3: Post Compression Evaluation Tests of Tablets

FORMULATION CODE	Muco adhesion Strength(g)	Muco adhesion Force(N)	Swelling index SI (%)	Matrix Erosion (%)	% Cumulative drug release
F1	12.277±0.11	1.69	68.2 ± 0.21	10.85 ±0.17	80.76±0.15
F2	14.497 ± 0.07	1.91	67.3 ± 0.19	10.55 ± 0.22	81.05±0.98
F3	15.852±0.06	2.04	65.8 ± 0.22	9.43 ± 0.21	86.15±0.54
F4	21.649±0.06	2.12	54.9 ± 0.18	9.12 ± 0.10	81.95±0.17
F5	23.218±0.03	2.12	50.3 ± 0.10	8.45 ± 0.18	92.15±0.15
F6	24.438±0.09	2.61	57.7 ± 0.22	9.86 ± 0.22	99.15±0.15
F7	19.766±0.08	1.93	65.4 ± 0.21	9.5.00 ± 0.19	78.00±0.17
F8	18.916±0.05	1.95	70.3 ± 0.17	10.45 ± 0.15	84.05±0.98
F9	15.852±0.06	1.64	62.8 ± 0.22	9.43 ± 0.21	87.55±0.54

Kinetic treatment to dissolution data

Kinetic studies i.e. zero-order, first order and Higuchi and Hixcon-Crowell were conducted for all formulations. The value of regression correlation co-efficient (R^2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero-order drug release.

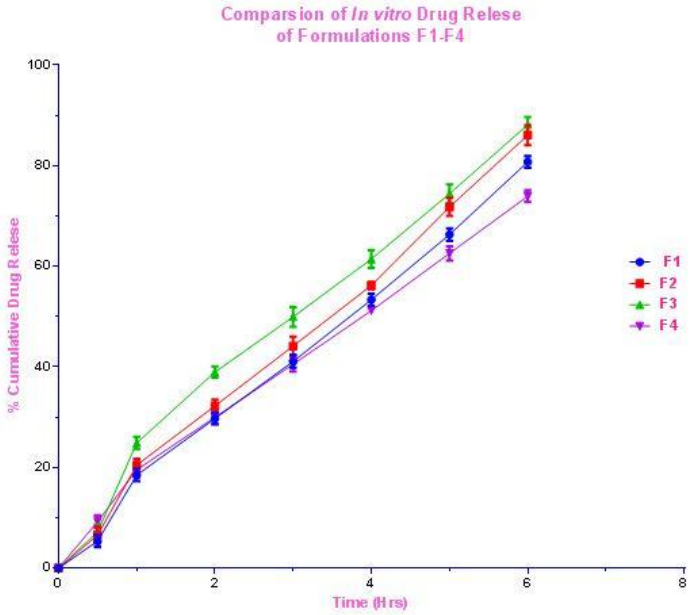

Fig. 1: Drug release Profile of formulations F1, F2, F3 &F4

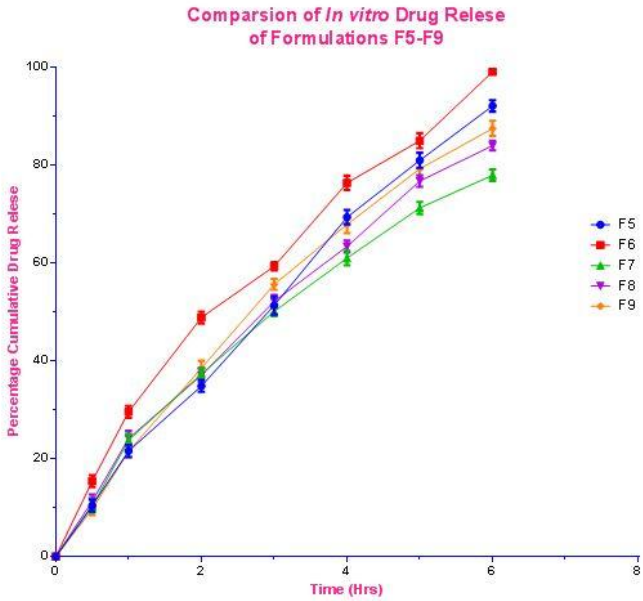

Fig. 2: Drug release profile of formulations F4, F5, F6, F7, F8 & F9

CONCLUSION

The overall studies indicated that the polymer Gum Olibanum showed satisfactory mucoadhesive properties. Among the 9 formulations, the formulation F6 using these polymer with drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation **F6** will be useful for buccal administration for the treatment of anti-hypertensive. So, the mucoadhesive buccal tablets of Losartan may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Losartan through Buccal mucosa.

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