Formulation And Evaluation of Olmesartan Mucoadhesive Buccal Patches

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Abstract— The main objective of the present study was to improve bioavailability of Olmesartan and decrease the frequency of dosage form administration by sustained release formulation of the drug from the mucoadhesive drug delivery system. Olmesartan belongs to the drug class known as an angiotensin II receptor (type AT) antagonist, orally active and undergoes first-pass metabolism by cytochrome P450 enzymes. It has an extensive and highly variable hepatic first pass metabolism following oral administration having half life of 10-15hr.The usual dose of Olmesartan is 10-20 mg twice daily with systemic bioavailability of 40- 50% due to extensive "first-pass" metabolism and has a narrow absorption window. These characteristics make Olmesartan a suitable drug candidate for mucoadhesive drug delivery system. Olmesartan containing mucoadhesive buccal patches were prepared by solvent Casting evaporation method. The buccal patches were formulated using polymers HPMC K 100 and Carbopol 934 alone and in combination. FTIR analysis of drug and excipients binary mixtures showed no interactions. The buccal patches were evaluated for weight variation, thickness, folding endurance, content uniformity, swelling index, in-vitro diffusion study, in-vitro residence time and in-vitro Mucoadhesive strength. Among nine formulations using factorial approach F4 showed maximum release 94.21% upto 8hr . Mucoadhesive buccal films of Olmesartan were successfully prepared and offers a promising alternative to oral delivery.

Index Terms— Olmesartan, HPMC K100M, Carbopol 934, Buccal mucosa, Mucoadhesive, Buccal film.

I. INTRODUCTION

Buccal drug delivery is an alternative to per-oral and parenteral administration of drug. To bridge the gap between the concept and the actual utilization of buccal delivery system in therapy, studies have been carried out which focus on assessing the feasibility of this delivery route and on developing delivery system for suitable drug candidates. The buccal mucosa lines the inner cheek and buccal formulations are positioned in the mouth, sandwiched between the gums and cheek to treat local and systemic conditions. The buccal route offers one of the potential routes for typically hydrophilic, large and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity is the preferred site for local and systemic drug delivery. Adhesion of bioadhesive formulation leads to increased concentration gradient of drug across absorption site and improves dosage form bioavailability.(1,2)

The antihypertensive, olmesartan is an angiotensin II receptor (type AT) antagonist, orally active and undergoes first-pass metabolism by cytochrome P450 enzymes.The terminal half-life of olmesartan is about 10-15 hr. Its log P and pka is 5.08 and 5.5 respectively. The drug is orally administered as 25 mg tablets once or twice daily with total daily doses ranging from 25 to 100 mg. Following oral administration, LP is well absorbed and undergoes substantial first pass metabolism; the systemic bioavailability of olmesartan is 33%. Thus to over-come extensive first-pass metabolism, olmesartan was selected as a candidate for formulation in a bioadhesive buccal patch.(3)

The present study involved formulation of buccal films using a factorial design with propylene glycol (PG), hydroxyl propyl methyl cellulose (HPMC) K100M and carbopol 934 as film formers and plasticizers and evaluating its ex vivo performance.

II. MATERIALS

Olmesartan was obtained as gift sample from Macleod pharma ,Mumbai and HPMC K100 from Colorcon Asia Pvt.Limited . Carbopol 934 & PVP K30 from Avience Chemicals and pharmaceuticals.other chemicals and the reagents used were of analyatical grade.

III. METHODS (3)

1) Infra- red Spectroscopy of drug

The procedure consisted of placing drug sample in FTIR sample holder. The drug sample was placed in the light path and scanned over the range of 4000- 400 cm-1 on Shimadzu FTIR prestige -21. The spectrum was recorded.

2. Compatibility studies

FTIR study was conducted to test the compatibility of the drug with excipients. The method consisted of placing the sample in the FTIR sample holder . On a Shimadzu FTIR prestige -21, the drug & excipient in the combination of binary mix in the ratio of 1:1 was placed in the light path and scanned across the region of 4000- 400 cm-1. The spectrum was taken down.

3. UV Spectroscopy (Determination of λ max)

a) Procedure for scanning

Preparation of standard solution of Olmesartan

Accurately weigh 25mg of Olmesartan and dissolved in 25ml with methanol (1000mcg/ml). from this solution pipette out 1ml and dilute to 10ml (100mcg/ml).

b)Scanning solution

The standard solution of 100 mcg/ml of olmesartan was scanned over the range of 200- 400nm against methanol as a blank using UV-Visible spectrophotometer. The lamba max for pure drug was then determined.

c)Calibration curve of Olmesartan :

From standard solution , 2, 4, 6 ,8, 10, and 12 ml was withdrawn in 10ml volumetric flask and dilute to 10ml with methanol to produce concentration of 20,40,60,80,100, and 120 mcg/ml respectively. The solution was analyzed by UV – Visible spectrophotometer at 253 nm and the result was recorded . The calibration graph was plotted as concentration on x axis and absorbance on y axis .

4. Solubility of Drug

To determine the drug solvent interaction solubility study was performed. Solubility study indicates effect on drug release and absorption of drug at various sites in vivo. Procedure: An excess amount of drug was added in different vials containing different solvents (10ml). The vials were ultrasonicated on ultrasonicater. Then the supernantant solution passed through a membrane filter and the amount of the drug dissolved was analyzed spectrophotometrically at 253 nm after suitable dilution

PREPARATION OF PATCH (7,8):

a)Preparation of ethyl cellulose backing layer

Ethyl cellulose (1 g) was dissolved in ethanol (5 ml) and a plasticizer of 5% propyleneglycol was added. The polymer solution was maintained for deaeration before being placed onto a petridish and covered with aluminium foil. The solution was held at room temperature for controlled solvent evaporation.

b)Formulation preparation

PVP K-30 was added after the drug had been dissolved in 10 mL of ethanol. Stirred until all of the contents were thoroughly dissolved, then added a weighed amount of HPMC K 100. Then, as a plasticizer, propylene glycol was added, and ethanol was used to get the volume up to 20 ml. The solution was then poured into a glass mould with a diameter of 12 inches and set away, covered with a funnel, to allow the solventto evaporate slowly.

c)Drying of patch

It is prepared at room temperature but this process required 2-3 days . Dried patches were cut into square $1*1cm^2$ size so that each patch contains about 10mg of drug. Patch should not be overdried or it should not contain moisture which will affect the physical properties of patch.

PRELIMINARY BATCH COMPOSITION:

Table 1. Preliminary bath composition

FORMULATION CODE	DRUG (mg)	PVPK-30(g)	HPMC K 100M(mg)	CARBOPOL 934P(mg)	ETHANOL (ml)	PROPYLENE GLYCOL (ml)
F1	502.4	1.25	100	100	20	2%
F2	502.4	1.25	150	150	20	3%
F3	502.4	1.25	250	300	20	4%
F4	502.4	1.25	100	300	20	5%
F5	502.4	1.25	400	100	20	1%
F6	502.4	1.25	200	200	20	7%
F7	502.4	1.25	100	200	20	2.5%
F8	502.4	1.25	200	100	20	4.5%
F9	502.4	1.25	400	300	20	1.5%

EVALUATION OF PRELIMINARY BATCH (9,10,11):

1) Thickness and Swelling index

Formulation code	Thickness(mm)	Swelling Index%
F1	0.19	17.26
F2	0.21	24.06
F3	0.22	32.00
F4	0.24	65.00
F5	0.28	54.27
F6	0.30	65.00
F7	0.31	52.00
F8	0.25	45.23
F9	0.33	41.87

Table 2. Evaluation of Thickness and Swelling Index

2) In-Vitro Study

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	19.34	25.34	28.60	15.08	10.76	7.70	11.20	15.20	12.30
1.5	42.61	53.45	49.87	20.19	16.17	11.28	16.54	19.32	15.62
2	75.29	82.16	79.54	27.99	20.15	17.18	19.87	22.56	24.89
2.5	95.21	91.59	90.52	41.87	25.27	23.67	25.14	28.63	35.62
3	-	96.30	96.30	52.47	36.79	27.97	35.42	34.85	41.26
3.5	-	-	-	61.94	42.56	34.80	44.56	38.12	52.89
4	-	-	-	72.61	48.30	39.64	52.31	47.89	65.45
4.5	-	-	-	84.61	62.34	46.06	59.81	56.34	70.23
5	-	-	-	94.21	77.29	60.52	61.81	59.34	75.53

Table 3. Evaluation of In-Vitro study

FACTORIAL DESIGN:

The objective of present investigation was to optimize the concentration of the polymers which showed sustained release of drug upto 10 hr. The data obtained from preliminary batches evaluation showed good result for F4 batch hence selected for 3^2 factorial designs.

Independent variable			
Level	-1	0	1
X1= amt of HPMC K100	100	200	400
X2=amt of Carbopol 934P	100	200	300

Table 4. The Independent Variable

The dependent variables are

1. In vitro dissolution study
2. Mucoadhesion time.

Formulation code	P1	P2	P3	P4	P5	P6	P7	P8	P9
X1 in mg	100	250	250	400	400	250	462	378.6	100
X2 in mg	300	341	200	300	100	58.57	200	200	100
Drug in mg	10	10	10	10	10	10	10	10	10
Propylene glycol %v/v	5	5	2	5	5	5	5	5	5

Table 5. Factorial Batches

EVALUATION OF FACTORIAL BATCH:

1) Weight of patch: The uniformity of weight for prepared buccal patches was analyzed by weighing the patches on the electronic balance (Shimadzu Corporation).

2) Folding endurance: A patch of 1x1 cm size was cut evenly and folded repeatedly at the same place till it brakes. The number of times of folding at the same place without breaking gives the value for folding endurance.(12)

3) Thickness: The thickness of the all-prepared patches was measured by using vernier caliper . The measurement was done at three different corners.

4) Surface pH study: The surface pH was measured by using pH meter. Initially the buccal patches were wet by 0.5 ml of water and allow equilibrating for 10 min. The digital Ph meter was dipped into the solution of patch and pH was recorded(12).

5) Disintegration time: It was done by visually analyzed in a petri dish with 2ml of distilled water by swirling after every 10s. The time taken by the patch to disintegrate orbreak is noted and recorded as invitro disintegration time.(16)

6) Drug content uniformity: The prepared patch was dissolved in the Ethanol and then absorbance was taken at 253 nm. Concentration of drug in the formulation was calculated using standard calibration curve of Olmesartan.(17)

7) Swelling index: The patch was weighed and placed on a pre-weighed cover slip. Thecover slip was then submerged in a petridish containing 20 ml phosphate buffer (pH6.8). Increase in weight of the film was determined at regular time intervals until a constantweight was obtained. The hydration ratio of the patch was calculated using followingformula. Where, W_t was weight of film at time t and W_0 was weight of film at zero time.(13,14)

% S= $(W_t-W_0/W_0)*100$

8) In vitro Dissolution drug release study: The dissolution studies were carried out by using USP TypeIIdissolution test apparatus (Lab India) in 300 ml of phosphate buffer having pH 6.8 at 37 ± 0.5^0 C and at 50 rpm. The patch was submerged into dissolution media and aliquot of 5 ml was withdrawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 and 5 minute time intervals. An equal volume of dissolution medium was added to the chamber after every withdrawal of aliquotto maintain the sink condition. The collected samples were analyzed spectrophotometrically at 253 nm using UV-Visible Spectrophotometer.(18)

9) Moisture Absorption study:-The moisture absorption studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulation maintains its integrity after absorption of moisture , 5%w/v agar in distilled water. In hot condition , was transferred into petriplates and it was allowed to solidify. One patches of each were selected and weighed. The patches were placed in dessicator overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane, They were placed on the surface of the agar and incubated at 37^0 C for 1hr in incubator. The patches were removed and weighed again .(15) The percentage of moisture absorbed can be calculated using the formula :

% Moisture absorbed= Final weight – Initial weight / Initial weight *100

RESULTS AND DISCUSSION

1) IR spectroscopy of drug : The observed IR peaks of Olmesartan matches the reported peaks.

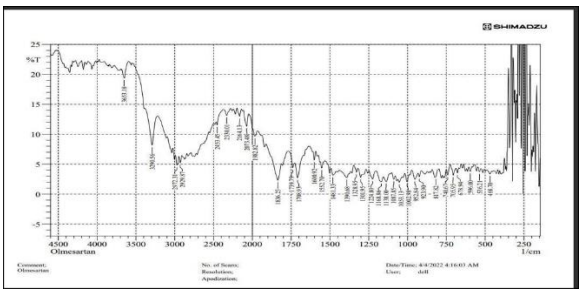

Fig 1. The IR spectra of Olmesartan

2) Compatibility Study: Studies of drug – excipient compatibility represents an important phase in the preformulation stage of formulation of buccal patch. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical,therapeutic properties and stability of the dosage forms.

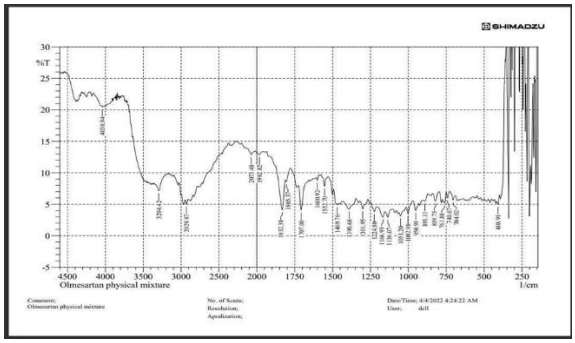

Fig 2. The IR spectra of Olmesartan +Polymer

3) UV Spectroscopy : The UV spectrum of the drug was obtained in methanol as asolvent which showed absorbance maximum at wavelength 253 nm which is same as the reported value.

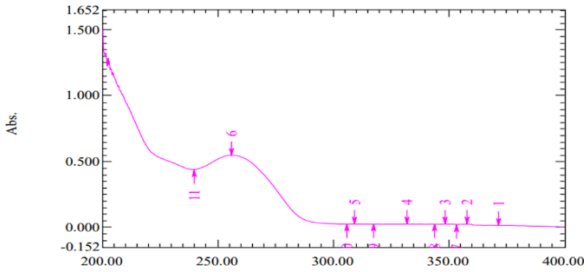

Fig 3. UV Spectra of Olmesartan

4) Solubility of drug Olmesartan: Olmesartan exhibited the low solubility in water and in acidic media ,whereas the high solubility in phosphate buffer(pH 6.8).

Fig 4.Solubility of drug

EVALUATTION OF FACTORIAL BATCH

a) Weight Variation Study: The average weight of buccal patches (F1 to F9) was determined. Result indicated thatthere was good uniformity of weight in patch. The average weight of patches (F1-F9) was found. Result is shown in Table 6.

b) Thickness Measurement: The average thickness of buccal patches (F1 to F9) was determined by Digital VernierCaliper. Results are shown in Table 6.

Sr no.	Medium	Solubility
1.	Water	Practically insoluble
2.	Methanol	Sparingly soluble
3.	Phosphate buffer (6.8)	Soluble
4.	Ethanol	Freely soluble
5.	Acetone	Insoluble
6.	Acetonitrile	Practically Insoluble

c) Surface pH study: The surface pH of buccal patches was found within the range. The pH of patch wasfound to be in the range of 6.2 to 7.6. Results are shown in Table 6. (22)

d) Content uniformity: The drug content uniformity of the patches was found to be in an average as theoretical value, Results are shown in Table 6.

e) Folding Endurance: Folding of the patches was done for about in between 172-200 times at same point.There was breaking of the patch found (20)

Parameter	P1	P2	P3	P4	P5	P6	P7	P8	P9
Weight(mg)	80mg	72.5mg	69mg	80.2mg	79.5mg	75mg	63mg	59mg	66.34mg
Thickness(mm)	0.26± 0.072	0.24± 0.052	0.25± 0.067	0.22± 0.091	0.27± 0.067	0.24± 0.073	0.26± 0.071	0.21±0. 067	0.22± 0.069
Surface pH	6.21± 0.44	6.43± 0.57	6.54± 0.55	6.79± 0.72	6.85± 0.69	6.98± 0.60	7.01± 0.62	7.26± 0.65	7.35± 0.52
Folding endurance	101± 1.13	93± 1.35	75± 1.37	60± 1.08	65± 1.61	70± 1.55	82± 1.30	78± 1.52	55± 1.23

%Moisture absorbance	167.56 ±1.56	169.35± 1.89	174.2± 1.54	178.35± 2.30	189.34± 1.25	191.56 ±1.85	196.24 ±1.45	198.58 ±1.63	201.56± 1.56
Mucoadhesion time(hr)	10.13± 0.23	8.74± 0.35	2.50± 0.45	2.18± 0.21	1.90± 0.56	2.47± 0.46	1.75± 0.55	2.40± 0.34	2.91± 0.65
Content uniformity(%)	98.76± 0.89	95.65± 0.79	96.35 ±1.18	94.67± 0.74	93.12± 1.31	94.90± 0.94	93.56± 0.92	95.35± 0.54	92.45± 0.72
Swelling index(%)	0.84± 0.06	0.45± 0.07	0.44± 0.07	0.60± 0.06	0.53± 0.05	0.55± 0.06	0.56± 0.02	0.43± 0.05	0.73± 0.02
Disintegration Time(sec)	35.6± 0.49	42± 0.69	22± 0.56	19± 0.63	20± 0.93	40± 0.58	29.2± 0.56	23.5± 0.68	37± 0.78

Table 5. Result of evaluation Parameters for

Factorial batch

f) Swelling Index: The Swelling index is one of the important physical parameters of buccal patch. The timefor swelling of mucoadhesive patch was recorded. (23)

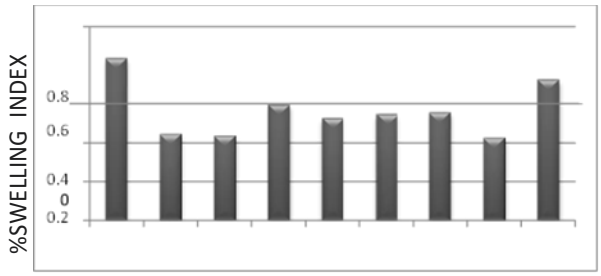

Fig.4 Graphical representation of %swelling index

g) Determination of in mucoadhesion residence time:

The mucoadhesive time is one of the important physical parameters of buccal patch. The time for complete erosion or detachment from the mucosa was recorded.

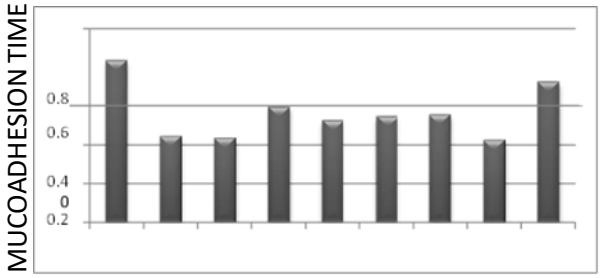

Fig 5. Graphical representation of mucoadhesion residence time

h) % Moisture Absorption:

The mucoadhesive time is one of the important physical parameters of buccal patch. The time for complete erosion or detachment from the mucosa was recorded.

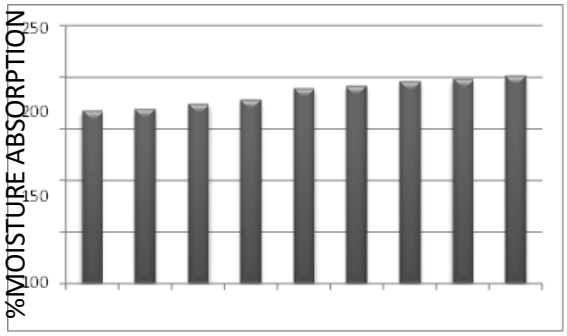

Fig. 6 Graphical representation of % moisture absorption

i) In vitro Dissolution study:

The percent cumulative drug release for P1 to P9 formulation is shown in Table 20. It was found that during dissolution there is sudden release of drug maximum upto 30% a first min. This is due to the fact that the drug is hydrophilic in nature as well as highly soluble in dissolution medium. If the amount of polymer increased in order to prevent sudden release of drug in first min. Increased in the concentration of HPMC K100, release of the drug get retarded due to high polymeric content. But as the concentration of Carbopol which is hydrophilic in nature increases, it enhanced the drug release.

The formulation P1 shows drug release 94.21% in 5 min this is due to increaseconcentration of HPMC

K100 present in patch. P2 showed drug release 83.57% and P3 have shown drug release upto 79.20% in 5 min. These increased in cumulative drug release is due to increase in the concentration of hydrophilic polymer, Carbopol 934 P. P4, P5, and P6 formulation showed drug release 65.42%, 58.87% and 75.91% in 5 min respectively. P7, P8 and P9 showed drug release 52.20%, 71.41%, and 88.42% in 5 minrespectively. These decreased in drug release is due to increased thickness of the gel layer formed by mucoadhesive polymer. In vitro drug release studies are shown in Table 6.

Table 6: In vitro drug release

Time (min)	Cummulative % Drug release from Factorial Batches								
	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0
0.5	17.03 ±0.81	11.60 ±0.9	15.32 ±0.80	22.46 ±0.70	16.35 ±0.76	20.30 ±0.73	25.08± 0.95	23.40± 0.45	20.80± 0.65
1	21.32 ±0.71	23.87 ±1.0	24.49 ±1.40	26.40 ±0.63	28.20 ±0.53	29.86 ±0.84	29.01± 1.13	26.81± 0.56	23.85± 0.92
1.5	26.30 ±0.56	29.33 ±0.71	30.20 ±0.59	33.46 ±0.94	37.81 ±0.90	38.80 ±0.95	33.40± 1.56	31.41± 0.89	29.20± 0.88
2	36.01 ±0.49	38.34 ±1.13	40.30 ±0.88	36.40 ±1.40	48.40 ±1.31	45.36 ±1.91	39.20± 1.23	42.05± 1.31	35.67± 1.23
2.5	36.50 ±1.31	43.36 ±1.56	51.21 ±1.23	42.72 ±1.19	54.61 ±1.16	51.62 ±1.47	43.21± 1.89	46.41± 1.59	48.68± 1.56
3	47.78 ±0.58	49.15 ±1.21	61.35 ±1.48	50.10 ±1.13	61.71 ±1.37	62.81 ±1.32	52.63± 1.65	54.66± 1.68	57.41± 1.89
3.5	50.51 ±1.21	54.73 ±1.41	65.07 ±1.09	56.81 ±1.34	72.21 ±1.27	74.83 ±1.56	57.01± 0.89	60.23± 1.97	66.41± 1.78
4	63.35 ±1.92	64.01 ±1.35	74.07 ±1.90	64.23 ±1.26	77.81 ±1.13	79.59 ±1.09	63.61± 1.45	68.65± 1.88	70.54± 1.97
5	94.21 ±1.33	83.57 ±1.60	79.20 ±1.34	65.42 ±1.81	58.87 ±1.51	75.91 ±1.83	52.20± 1.87	71.41± 0.56	88.42± 1.49

All values are expressed in mean ±SD(n=3)

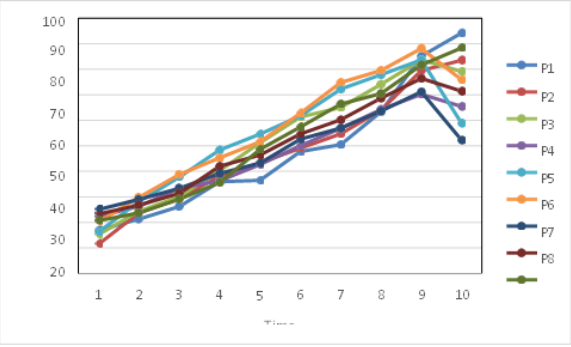

Fig.7 Drug release profile of P1to P9

FACTORIAL DESIGN SUMMARY:

The 3^2 full factorial design was applied to study the effects of independent variables such as HPMC K100M% (X1) and Carbopol934P %(X2) on dependent variables such as mucoadhesion strength , Mucoadhesion Time, % drug release at 10hr.

Table 7: Summary of statistical design

Factor	Name	Unit	Type	Actual values		Coded values	
				Low	High	Low	High

A	HPMC K100M	mg	Numeric	100	400	+1	-1
B	Carbopol 934P	mg	Numeric	100	300	-1	+1

Table 8: Summary of response.

Response	Name	Units	Obs	Analysis	Min	Max	Mean
Y1	Mucoadhesion Time	hr	9	Polynomial	1.75	3.13	2.44
Y2	Drug release	%	9	Polynomial	52.2	9.21	73.205

Table 9: Analysis of variance for Mucoadhesion Time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.13	2	0.5667	6.87	0.0281	significant
A-HPMC K100M	1.04	1	1.04	12.56	0.0122	
B-CARBOPOL	0.0972	1	0.0972	1.18	0.3193	
Residual	0.4949	6	0.0825			
Cor Total	1.63	8				

Factor coding is Coded.
Sum of squares is Type III - Partial

The Model F-value of 6.87 implies the model is significant. There is only a 2.81% chance that an F-value this large could occur due to noise.

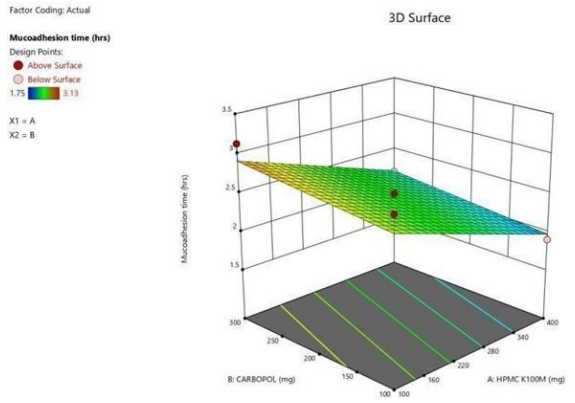

Fig 8. Response surface plot of mucoadhesion time

Source	Sum Zof Squares	df	Mean Square	F-value	p-value	
Model	981.05	2	490.53	5.44	0.0449	significant
A-HPMC K100M	913.93	1	913.93	10.14	0.0190	
B-CARBOPOL	67.12	1	67.12	0.7445	0.4214	
Residual	540.94	6	90.16			
Cor Total	1521.99	8				

Table 10 : Analysis of Variance for Drug Release

Factor coding is Coded.
Sum of squares is Type III - Partial

The Model F-value of 5.44 implies the model is significant. There is only a 4.49% chance that an F-value this large could occur due to noise.

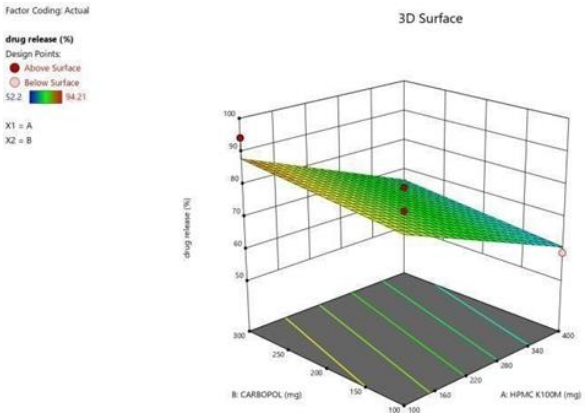

Fig.9 Response surface plot of % drug release at 10 hr.

CONCLUSION

The buccal patches offer many advantages for the drug which get degraded by the otherroute of administration mostly by oral routes. Similarly buccal route provides for faster set of action and if designed properly can be used for sustaining the release of the drug Olmesartan is most commonly used as an antihypertensive agent . If the dosage form is designed in sustain release it provides more advantage for the antihypertensive therapy.

The objective of work was to formulate buccal patches of Olmesartan using combination of hydrophilic polymers such as Hydroxypropyl methylcellulose and Carbopol 934 P . The mucoadhesive patch formulation itself is a critical process hence it requires optimization at various stages.

First stage was the optimization of formulation . This study reveals that the hydrophilic polymers have good patch forming properties with varying amount. With the change in amount of polymers, patch thickness gets change. Second stage was the optimization of the plasticizer concentration in the patch. Propylene glycol was used as plasticizer. Plasticizer in the patch helps to maintain the flexibility and its integrity hence optimization was needed. After study it was found that 5% of the concentration was found to be optimized which gave good physical properties of the patch. Next stage was the optimization of drying time. Drying time is an important factor in formulation development. The patch was dried at room temperature, then it required about 2 to 3 days.

Various Preformulation studies showed that drug had its purity and authenticity. Compatibility study gave the assurance that drug and various polymers used in the formulation were compatible with each other. Analytical method validation was done inmethanol . Next stage is the preparation of preliminary batches F1 to F9 and evaluated for swelling index, and in vitro drug release study, thickness, weight measurement. Among the Six batches F4 was selected for factorial which gave the highest drug releasein 5 min.

A systematic study using 3^2 factorial design was applied to optimize the formulation . The study revealed that the amount of HPMC K100M and Carbopol 934P has significanteffect on mucoadhesive properties such as swelling index, mucoadhesive strength , and mucoadhesion time, and release characteristics of the drug.

From results, it can be concluded that formulation P1 had mucoadhesive properties. In vitro cumulative % drug release of formulation P1 was found to be 94.21% upto 5 min. Swelling index was found to be 80.10%. and % moisture absorption was found to be 167.35%. Response surface methodology study was carried out for in vitro drug release. It was found that the composition of hydrophilic and hydrophobic polymer concentration plays a very important role in various buccal patch evaluation parameters because of their mucoadhesive and release controlling properties.

Thus, Olmesartan buccal patches releasing drug upto 10 hr can be successfully formulated which can be comfortably used by the patients with improved bioavailability with sustained release characteristics. However, there is need for further in vivo and stability studies.

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