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FORMULATION AND EVALUATION OF BUCCAL PATCHES OF TRAMODOL HYDROCHLORIDE

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ABSTRACT

The goal of present investigation highlights the formulation and evaluation of mucoadhesive buccal patches of Tramadol hydrochloride. The mucoadhesive buccal patches of Tramadol hydrochloride were prepared by solvent casting technique using various combinations of polymers like HPMC E15, Carbopol 934, Carboxy Methyl Cellulose Sodium, Poly vinyl Alcohol and PVP K30. In the present study, total nine formulations were subjected to various evaluation parameters. Based on the evaluation results, it was concluded that drug content uniformity was varied between 75.5% (C5) and 98.6% (B2). Batch B showed higher drug loading as compared to Batch A and Batch C. Swelling was found to be greatest in batch B, followed by batch C and batch A respectively. Swelling increased with increase in concentrations of PVP, PVA, HPMC and Na CMC but was found to be inversely proportional to concentrations of Carbopol. It was also evaluated from the results that maximum *in-vitro* release was 94.07% (**A9)** over a period of 120 minutes for Batch A. For Batch B maximum release was evaluated to be 93.75% (**B5)** while for Batch C, it was found to be 98.3% (**C4)** after 120 minutes.

KEYWORDS: Buccal patch, solvent casting technique, *in-vitro* release, swelling index, Tramadol Hydrochloride.

INTRODUCTION

Amongst the Various routes of administration, oral route is the most preferred route because of the patient compliance but also have several disadvantages as first pass metabolism, enzymatic degradation within the GI tract which leads to low bioavailability.[1] Therefore, other absorptive mucosae is considered as potential site for the administration of drug. Transmucosal route for drug delivery offers a various advantages over oral drug delivery system.[2]

Buccal drug delivery is the most attractive route of administration as buccal mucosa has excellent accessibility, expanse of smooth muscle and relatively immobile mucosa which directly access into the systemic circulation through internal jugular vein leading to higher bioavailability.[3] The drug is delivered in various forms like gel, tablet, patch, film, lozenges, wafers etc but among these, buccal patch have been reported to be the most promising area and effective approach for drug delivery through epithelium with higher patient compliance.[4]

Tramadol acts as a μ-opioid receptor antagonist, serotonin releasing agent, nor epinephrine reuptake-inhibitor, NMDA- receptor antagonist, $5HT_{2C}$ receptor antagonist and M_1 &M_3 muscarinic acetylcholine receptor antagonist. The analgesic action of Tramadol is believed to work through modulation of serotonin and nor-epinephrine in addition to its relatively weak μ-opioid receptor antagonist. The contribution of non-opioid activity is demonstrated by the fact the analgesic effect of Tramadol is not fully antagonized by the μ – opoiod receptor antagonist naloxone. Tramadol's primary active metabolite, *O*-desmethyltramadol, is a considerably more potent μ-opioid receptor agonist than tramadol itself. Thus, tramadol is in part a prodrug to *O*-desmethyltramadol.[5,6]

The present study was to develop evaluate mucoadhesive buccal patches containing tramadol hydrochloride as a drug using different ratios of hydrophilic polymers to avoid hepatic first pass metabolism and to increase bioavailability of the drug. Tramadol HCL was chosen as a a model drug for study since it posses ideal characteristics that drug must have in formulating Buccal drug delivery system such as low molecular weight and high lipid solubility.

MATERIAL AND METHOD

Tramadol HCL as a gift sample from K Pharma, Ambala. Carbopol 934, Carboxy Methyl Cellulose Sodium, Poly vinyl Alcohol, Potassium dihydrogen orthophosphate and Propylene glycol was obtained from Loba-Chemie Pvt. Ltd., Mumbai. Disodium hydrogen phosphate and PVP K30 were procured from Himedia Laboratories Limited, Mumbai respectively. HPMC E15and Sodium

Chloride was obtained from S.D. Fine-Chem Limited, Mumbai.

METHOD

The buccal patches of Tramadol HCl were prepared by solvent casting method using different combinations of various hydrophilic polymers like HPMC, Sodium CMC, Carbopol 934 and PVP K30. PVA was used as film forming polymer and PG as plasticizer. Drug was accurately weighed and dissolved in 2 ml of distilled water in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The glass mould covered with foil was placed over a flat surface. The whole solution was poured into the glass mould. Inverted funnel was placed over the mould to avoid sudden evaporation. The mould containing polymeric solution of drug was kept 24 hours at 50º C for drying. After drying, the films were observed and checked for possible imperfections upon their removal from the moulds. They were packed in aluminium foil and preserved in desiccator till the evaluation tests were performed.[7] Table 1 shows the various composition of buccal patches.

Table 1- Composition of various patch formulations

Formulation code	Polymers					Plasticizer	Drug
	PVA (mg)	HPMC (mg)	CP (mg)	PVP K30 (mg)	Na CMC (mg)	Propylene glycol(mL)	Tramadol HCl(mg)
A1	400	300	50	-	-	2	50
A2	450	250	50	-	-	2	50
A3	350	350	50	-	-	2	50
A4	350	300	100	-	-	2	50
A5	400	250	100	-	-	2	50
A6	300	350	100	-	-	2	50
A7	300	300	150	-	-	2	50
A8	350	250	150	-	-	2	50
A9	250	350	150	-	-	2	50
B1	400	-	-	300	50	2	50
B2	450	-	-	250	50	2	50
B3	350	-	-	350	50	2	50
B4	350	-	-	300	100	2	50
B5	400	-	-	250	100	2	50
B6	300	-	-	350	100	2	50
B7	300	-	-	300	150	2	50
B8	350	-	-	250	150	2	50
B9	250	-	-	350	150	2	50
C1	400	300	-	-	50	2	50
C2	450	250	-	-	50	2	50
C3	350	350	-	-	50	2	50
C4	350	300	-	-	100	2	50
C5	400	250	-	-	100	2	50
C6	300	350	-	-	100	2	50
C7	300	300	-	-	150	2	50
C8	350	250	-	-	150	2	50
C9	250	350	-	-	150	2	50

EVALUATION[7,8,9]

1. Uniformity of weight of the patches

Patches sizes of 2x2 cm^2 were cut. The weights of three patches were taken and the weight variation was calculated.

2. Thickness uniformity of the patches

The thickness of each patch was measured using vernier calliper at five different positions of the patch and the average was calculated.

3. Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times without breaking. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on three patches.

4. Drug Content Uniformity

It was determined by dissolving the patch ($2cm^2$) from each batch in 100 ml simulated salivary fluid (pH 6.8) for 6 hrs under magnetic stirring. The 5 ml resultant solution was adequately diluted, filtered through whatman filter paper and drug content measured at 271 nm using UV-Vis spectrophotometer.

5. Surface pH

The surface pH values of the patch formulations were determined to evaluate the possible irritation effects on the mucosa. The films were left to swell in 5ml of simulated salivary fluid (pH 6.8) in small beakers. The pH was measured at time intervals of 15, 30 and 60 min. by placing the electrode in contact with the surface of the swollen patches. The average pH of three determinations was reported.

6. Swelling studies of the patches

Film sample was weighed and immersed in 50 ml of simulated salivary fluid of pH 6.8. The increase in weight of film was noted in 15 min intervals for 60 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch. The percent swelling, % S.I., was calculated using the following equation:

$$\% \text{ S.I.} = \frac{Wt - Wo}{Wo} \times 100.$$

Where, Wt- weight of the swollen patch after time t and
Wo- original patch weight at zero time

7. In vitro release studies

The release study was carried out in a USP dissolution apparatus type 1, slightly modified in order to overcome small volume of the dissolution medium. The dissolution medium was 150ml simulated salivary fluid, pH 6.8, maintained at 37±0.5ºC and kept in a glass beaker fixed inside the dissolution flask. The patch was fixed to the central axis, which rotates at 50 rpm. Filtered samples (5 ml) were manually collected at intervals of 5, 10, 15, 30, 60, 90, 120 and 180 minutes. The samples were compensated with equal volume of simulated salivary fluid kept at same temperature. The concentration of release medium was assayed spectrophotometrically at 271 nm after suitable dilution with dissolution medium, if necessary.

RESULT AND DISCUSSION

1. Uniformity of weight of the patches

Drug loaded patches (2 cm^2) were tested for uniformity of weight. The patches were found uniform in weight. The average weight of the different batches of patches varied between 0.081 g and 0.16 g.

2. Thickness uniformity of the patches

All patches showed uniformity in thickness at various places in the same patch. The thickness of medicated patches of diverse batches ranged between 0.1 and 0.3 mm.

3. Folding endurance

Films did not show any visible cracks even after folding upto more than 200 times in all types of formulations. Hence it was taken as the end point.

4. Drug Content Uniformity

The results of content uniformity indicated that the drug was uniformly dispersed and patches showed favourable drug loading which varied between 75.5% (C5) and 98.6% (B2). Batch B showed higher drug loading as compared to Batch A and Batch C.

5. Surface pH

The surface pH of all patches ranged from 6-7 and hence no mucosal irritation was expected.

Table 2: Evaluation parameters of prepared buccal mucoadhesive patches

Formulation code	Average weight (gm)	Thickness (mm)	Folding endurance	% Drug content	Surface pH
A1	0.127	0.302	>200	79.9	6.3
A2	0.121	0.306	>200	96.7	6.5
A3	0.145	0.338	>200	89.2	6.7
A4	0.153	0.338	>200	88.1	7.0
A5	0.17	0.305	>200	76.5	6.0
A6	0.105	0.239	>200	87.01	6.4
A7	0.106	0.269	>200	79.3	7.0
A8	0.163	0.271	>200	84.3	6.3
A9	0.131	0.206	>200	82.2	6.5
B1	0.128	0.304	>200	91.4	6.1
B2	0.096	0.201	>200	98.6	6.5
B3	0.098	0.201	>200	94.5	6.6
B4	0.093	0.205	>200	87.28	7.0
B5	0.093	0.207	>200	92.3	6.4
B6	0.095	0.207	>200	88.1	6.4
B7	0.085	0.203	>200	92.2	6.8
B8	0.122	0.301	>200	82.3	6.7
B9	0.106	0.239	>200	95.3	6.5
C1	0.121	0.238	>200	79.09	6.2
C2	0.097	0.203	>200	93.1	6.4
C3	0.102	0.203	>200	79.75	6.8

C4	0.117	0.205	>200	77.9	6.4
C5	0.133	0.237	>200	75.5	6.5
C6	0.112	0.205	>200	84.2	6.8
C7	0.126	0.202	>200	84.6	7.0
C8	0.134	0.206	>200	86.1	6.4
C9	0.124	0.304	>200	91.6	6.1

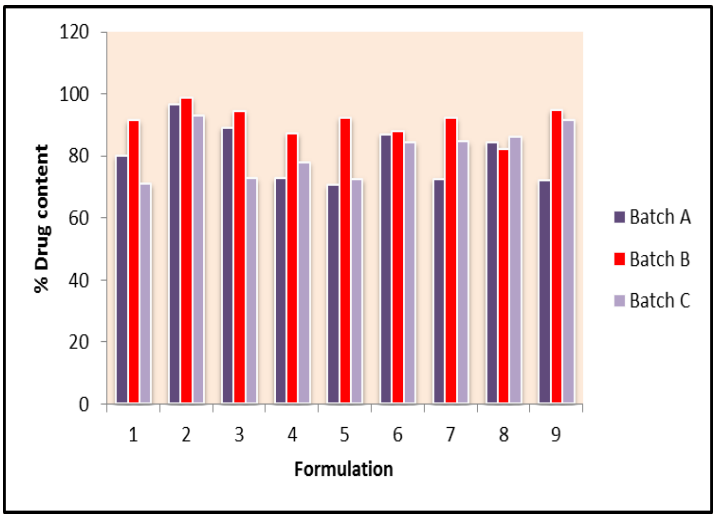

Fig. 1- Graphical representation of % drug content of all batches

6. Swelling studies of the patches-

The swelling of the patches were observed in simulated salivary fluid (pH 6.8) and the results are shown in the table.

Table 3- Swelling index of various formulations at different time intervals

Formulation code	15 min	30 min	45 min	60 min
A1	12	28.8	39.2	48
A2	12.5	30.14706	41.91176	50.73529
A3	33.03571	37.5	43.75	56.25
A4	19.29825	37.7193	42.98246	47.36842
A5	18.03279	33.60656	40.16393	49.18033
A6	31.57895	45.26316	50.52632	56.84211
A7	23	36	45	50.5
A8	12.09677	15.32258	25	43.54839
A9	20.98765	40.74074	48.14815	51.85185
B1	21.17647	42.35294	51.76471	55.29412
B2	19.08397	35.87786	45.80153	56.48855
B3	23.27586	43.96552	51.72414	57.75862
B4	21.57895	34.73684	38.42105	56.84211
B5	20.77922	25.32468	46.1039	57.79221
B6	29.93197	44.89796	57.14286	61.22449
B7	12.29947	31.01604	50.26738	54.54545
B8	23.89937	43.39623	48.42767	56.60377
B9	16.99346	26.14379	49.6732	60.13072
C1	18.46154	31.53846	42.30769	50.76923
C2	20.22472	33.70787	39.32584	48.31461
C3	20	30.47619	37.14286	51.42857
C4	22.22222	39.50617	43.20988	54.32099
C5	24.24242	33.33333	39.39394	48.48485
C6	27.77778	43.33333	55.55556	61.11111
C7	17.72152	31.64557	40.50633	55.6962
C8	21.37931	30.34483	33.10345	45.51724
C9	13.7931	35.34483	43.10345	56.03448

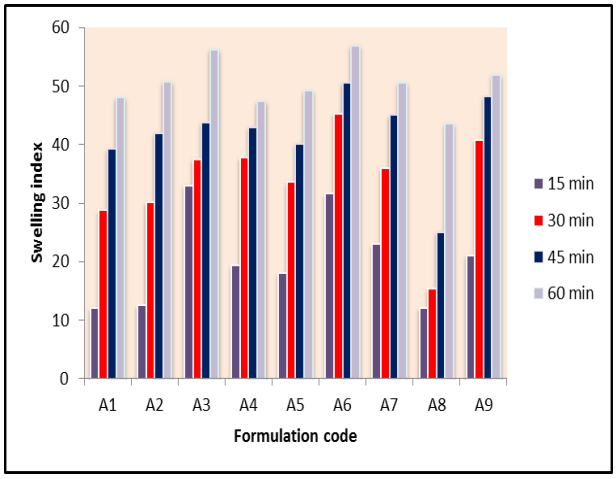

Fig. 2- Graphical representation of solubility index of Batch A at different time intervals

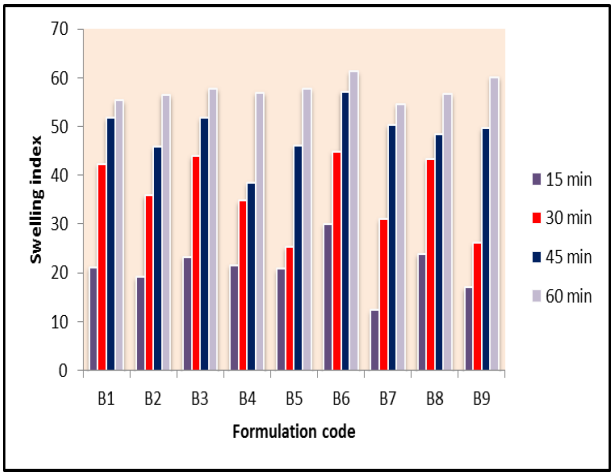

Fig. 3- Graphical representation of solubility index of Batch B at different time intervals

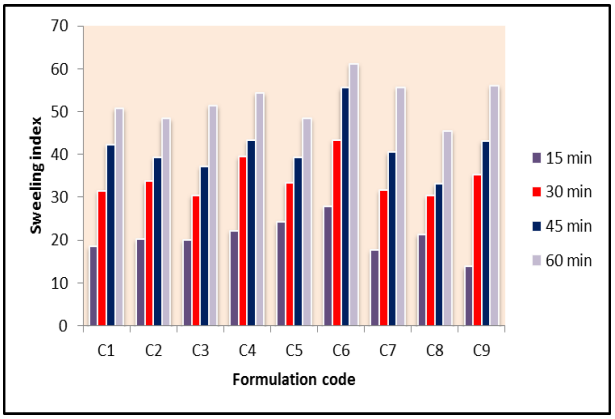

Fig. 4- Graphical representation of solubility index of Batch C at different time intervals

Swelling was found to be greatest in batch B, followed by batch C and batch A respectively. Swelling increased with increase in concentrations of PVP, PVA, HPMC and Na CMC but was found to be inversely proportional to concentrations of Carbopol. Higher swelling indices may be attributed to the presence of water-soluble polymers. Even though the swelling was high, the patches did not show any appreciable change in shape and form and maintained integrity during the study period.

7. In-vitro release studies

In-vitro release studies of all formulations were performed using pH 6.8 simulated salivary fluid as dissolution medium and measuring drug concentration spectrophotometrically at 271 nm. The cumulative percent of drug release at different time intervals are shown in table.

Table 4- % Cumulative Drug Release of batch A1-A4 at various time intervals

Time (min.)	A1	A2	A3	A4
0	0	0	0	0
5	30.45	27.76	32.63	34.86
10	45.31	41.09	52.47	59.05
15	61.99	60.38	60.39	71.33
30	71.24	69.18	73.13	73.36
60	77.46	80.62	75.63	76.38
90	82.80	91.42	78.13	78.12
120	81.39	92.86	81.69	80.81
180	80.94	91.50	81.45	80.24

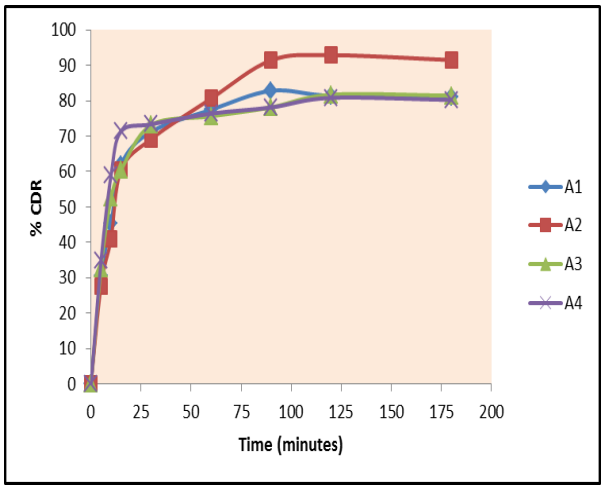

Fig. 5- Graphical representation of % CDR of A1-A4 at different time intervals

Table: 5 % Cumulative Drug Release of batch A5-A9 at various time intervals

Time (min.)	A5	A6	A7	A8	A9
0	0	0	0	0	0
5	33.90	29.32	25.56	28.15	26.62
10	47.41	43.28	44.88	36.83	36.38
15	64.33	48.04	53.55	54.41	58.66
30	75.50	59.72	79.86	75.10	67.88

60	78.50	68.76	82.62	89.38	82.44
90	81.84	75.30	84.58	86.74	85.62
120	80.76	84.64	85.59	86.33	94.07
180	79.84	83.99	84.20	86.32	92.16

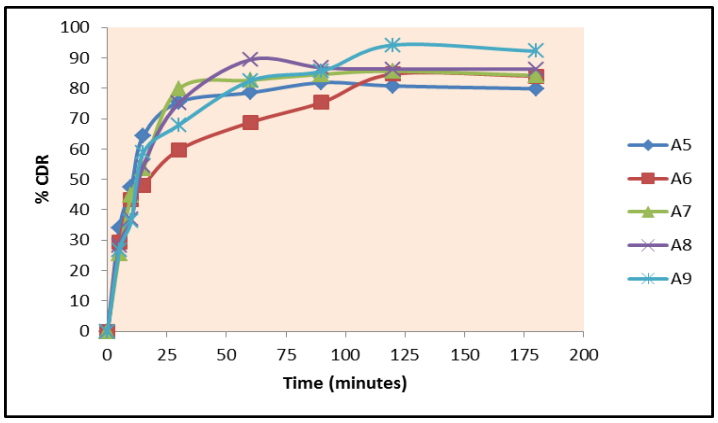

Fig. 6- Graphical representation of % CDR of A5-A9 at different time intervals

Table 6- % Cumulative Drug Release of batch B1-B4 at various time intervals

Time (min.)	B1	B2	B3	B4
0	0	0	0	0
5	28.33	29.68	28.45	30.82
10	35.94	39.01	38.23	39.98
15	45.33	61.16	46.86	50.52
30	53.55	70.22	58.91	60.28
60	67.56	85.08	73.04	71.30
90	84.69	91.68	82.33	83.86
120	83.16	90.99	92.98	81.90
180	81.84	88.87	91.80	77.98

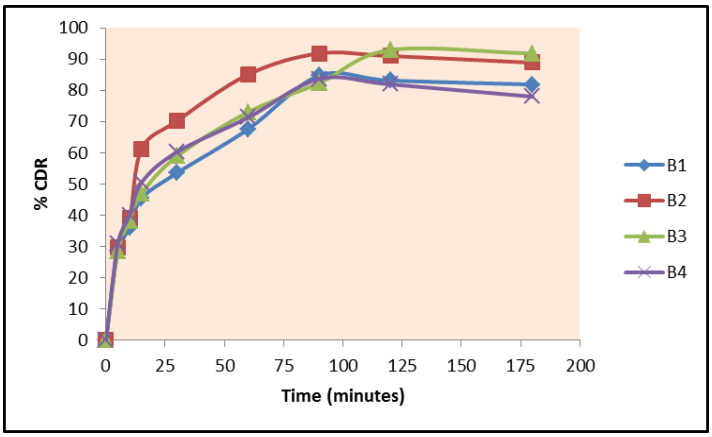

Fig. 7- Graphical representation of % CDR of B1-B4 at different time intervals

Table 7- % Cumulative Drug Release of batch B5-B9 at various time intervals

Time (min.)	B5	B6	B7	B8	B9
0	0	0	0	0	0
5	26.35	33.03	23.23	26.73	31.65
10	41.16	47.53	37.63	28.75	42.04
15	51.41	57.35	48.10	34.81	47.22
30	65.29	69.27	58.45	44.42	61.99
60	76.29	74.56	68.80	56.41	74.25
90	86.43	89.46	78.59	65.08	82.44
120	93.75	88.61	77.85	83.38	81.80
180	92.63	87.23	75.42	82.15	79.34

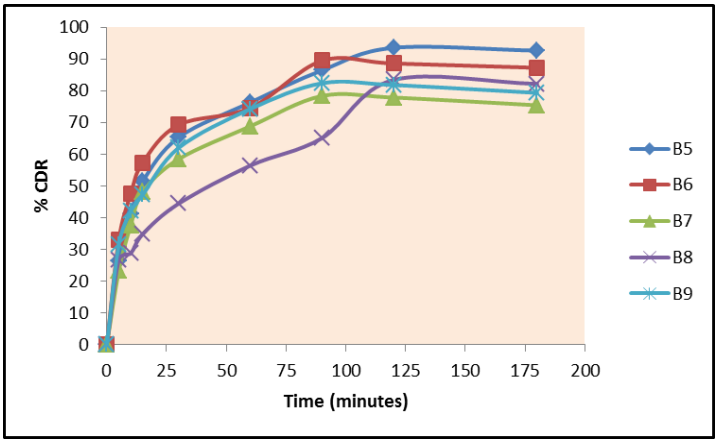

Fig. 8- Graphical representation of % CDR of B5-B9 at different time intervals

Table 8- % Cumulative Drug Release of batch C1-C4 at various time intervals

Time (min.)	C1	C2	C3	C4
0	0	0	0	0
5	32.42	30.20	25.02	28.01
10	42.87	37.46	40.66	37.03
15	52.95	49.13	57.49	45.92
30	64.60	61.49	72.84	60.21
60	72.01	68.66	83.04	74.69
90	82.50	74.1	85.92	88.09
120	81.57	70.62	87.93	98.32
180	78.41	69.46	86.56	95.85

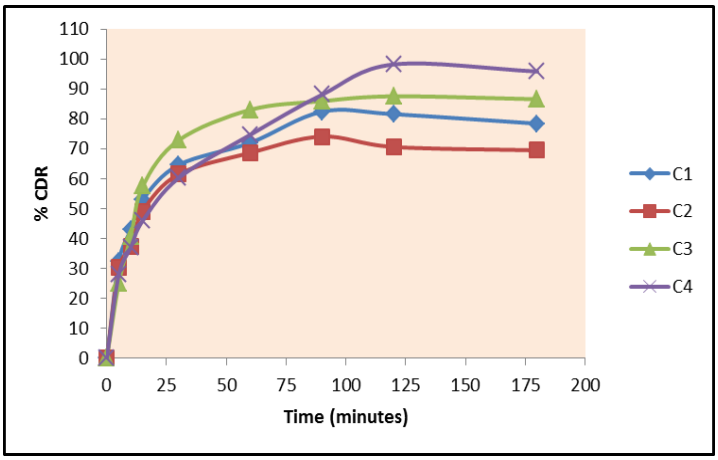

Fig. 9- Graphical representation of % CDR of C1-C4 at different time intervals

Table 9- % Cumulative Drug Release of batch C5-C9 at various time intervals

Time (min.)	C5	C6	C7	C8	C9
0	0	0	0	0	0
5	26.94	29.89	30.62	28.21	30.30
10	50.46	44.47	47.89	34.51	43.15
15	62.53	56.47	63.43	44.69	59.17
30	75.84	65.01	74.56	56.45	77.21
60	81.66	79.55	83.66	68.61	85.84
90	91.00	88.17	95.26	81.51	88.47
120	90.76	97.68	91.20	91.57	91.02
180	89.13	90.78	93.56	93.19	87.23

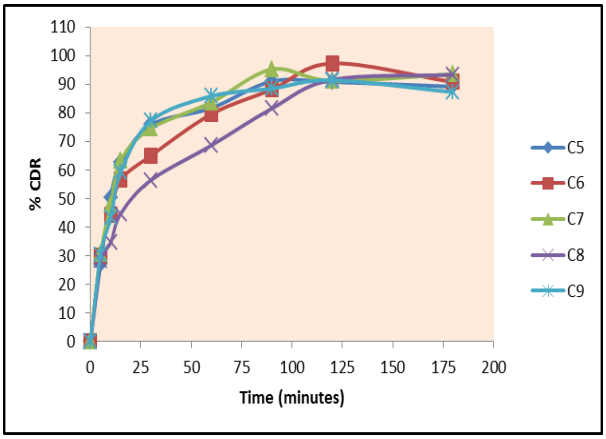

Fig. 10- Graphical representation of % CDR of C5-C9 at different time intervals

It was evaluated from the results that maximum in-vitro release was 94.07% (**A9)** over a period of 120 minutes for Batch A. For Batch B maximum release was evaluated to be 93.75% (**B5)** while for Batch C, it was found to be 98.3% (**C4)** after 120 minutes. It was noted that increase in concentration of hydrophilic polymer led to increase in % CDR for Batch A. For Batch B and C, there was increase in % CDR with increment in polymer concentration but upto an extent after which % CDR decreased. It was also observed that batches A and C showed maximum release over 120 minutes while for batch B the most number of highest% CDR were over 90 minutes. The high drug release could be explained by the ability of hydrophilic polymers to absorb water, thereby promoting dissolution, and hence the release of highly water-soluble drug tramadol hydrochloride. Moreover, hydrophilic polymers would dissolve creating more pores and channels for the drug to diffuse out of the patches.

CONCLUSION

The objective of the study was to formulate buccal patches of Tramadol Hcl using various combinations of hydrophilic polymers such as HPMC E15, Carbopol 934, Carboxy Methyl Cellulose Sodium, Poly vinyl Alcohol and PVP K30 to avoid hepatic first pass metabolism and to increase bioavailability of the drug. It was noted that increase in concentration of hydrophilic polymer led to increase in % CDR for Batch A. The results of content uniformity indicated that the drug was uniformly dispersed and patches showed favourable drug loading which varied between 75.5% (C5) and 98.6% (B2). Batch B showed higher drug loading as compared to Batch A and Batch C. The present study indicated potential of mucoadhesive buccal patches containing Tramadol HCl for systemic as well as local delivery with weak opioid agonist properties has been proved to be effective without causing serious side FF effects in both experimental and clinical pairs.

REFERENCES

1. Koyi P, Khan A, Buccal Patches: A Review. Int. J. Pharm. Sci. Res, 2013; 4(1): 83-89.
2. Sharma N, Jain S, Sardana S. Buccoadhesive drug delivery system: A Review. J. Adv. Pharm. Edu. Res., 2013; 3(1): 1-15
3. Sudharkar Y, Kuotsu K, Bandyopadyay AK. Buccal bioadhesive buccal drug delivery: A promising option for orally less efficient drugs. J. Controlled Release, 2006; 114: 15-40.
4. Verma S, Ashima, Singh R. Buccal patches: A radical approach in transmucosal drug delivery. Indo Am. J. Pharm. Res, 2016; 6(4): 5181-5192.
5. http://www.lookchem.com/Tramadol-hydrochloride/
6. http://en.wikipedia.org/wiki/Tramadol
7. Puratchikody A, Prasanth VV, Mathew ST, Kumar AB. Development and characterization of mucoadhesive patches of salbutamol sulphate for unidirectional buccal drug delivery. Acta Pharm, 2011; 61: 157-170.
8. Chimmiri P, Rajalakshmi R, Ramesh G.Design and characterization of buccal films of tramadol hydrochloride. Int J Bio Pharm Res., 2012; 3(3): 347-353.
9. Verma N, Ghosh AK, Chattopadhyay P. Preparation and evaluation of mucoadhesive buccal patches containing metoprolol succinate. Int J Ph Sci., 2011; 3(1): 1075-1079.