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Der Pharmacia Lettre, 2018, 10 [4]: 126-140
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ISSN 0975-5071
USA CODEN: DPLEB4

Formulation, Optimisation and Qualtiy Control of Diacerein Loaded Buccal Strips

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ABSTRACT

The current research work deals with the formulation and evaluation of diacerein loaded buccal strips followed by optimization and quality control. Diacerein is also known as diacetylrhein, is a slow-acting drug which belongs to anthraquinone class and is used to treat joint diseases such as osteoarthritis. It works by inhibiting interleukin-1 beta. Ten bathces of buccal atrips were prepared using polymers like HPMC, Eudragit, sodium alginate, and sodium CMC in varying proportions. A total amount of upto 4% of the polymers were used in combination. The amount 4% wwas optimized by trial batches ranging from 0.5% to 6% of the polymer amount. All the formulations were subjected for quality control parameters like folding endurance, content uniformity, swelling index, surface pH, mucoadhesive strength studies, invitro permeation, ex vivo permeation and stability studies. The results were analysed and on the basis of the resullts optimized formulations was selested. The prepared formulations showed zero order controlled release following super case II transport mechanism suggesting controlled release by swelling and erosion mechanism. The formulations were found to be stable and good platform for management of osteoarthritis.

Keywords: Diacerein, Buccal strips, Mucoadhesive.

INTRODUCTION

The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. It is also possible to administer drugs to patients who unconscious and less co-operative. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with various combinations of polymers, absorption enhancers.[1] Natural polymers have recently gained importance in pharmaceutical field. Mucoadhesive polymers are used to improve drug delivery by enhancing the dosage form's contact time and residence time with the mucous membranes. Mucoadhesion may be defined as the process where polymers attach to biological substrate or a synthetic or natural macromolecule, to mucus or an epithelial surface. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion [2] The substrate possessing bioadhesive polymer can help in drug delivery for a prolonged period of time at a specific delivery site. The studies of Mucoadhesive polymers provide a good approach of mucoadhesion and some factors which have the ability to affect the mucoadhesive properties of a polymer. Both natural and synthetic polymers are used for the preparation of mucoadhesivebuccal patches. In addition to this, studies have been conducted on the development of controlled or slow release delivery systems for systemic and local therapy of diseases in the oral cavity [3,4].

Advantages

1. It is richly vascularized and additional reachable for administration and removal of formulations.
2. Patient accessibility is high.
3. Retentive dosage forms are suitable for administration.
4. Improves bioavailability by eliminating first pass metabolism.
5. Surface of buccal mucosa achieves a fast cellular recovery.
6. Low enzyme activity.
7. Non-invasive method of drug administration.
8. Ability to incorporate permeation enhancer in the formulation

Diacerein is also called diacetylrhein, is a slow-acting medicine of the anthraquinone class used to treat joint diseases such as osteoarthritis. It works by blocking the actions of interleukin-1 beta which is a protein involved in the inflammation and degradation of cartilages that play a significant role in development of symptoms of degenerative diseases of the joints such as osteoarthritis. It has a specific mode of action in which it does not involve the inhibition of prostaglandin synthesis but it has been shown to have anti-osteoarthritis and cartilage stimulating properties in vitro and animal models [5].

The rationale for selecting diacerein and formulating its buccal patches is that it belongs to BCS class II and has low solubility which causes low absorption and low oral bioavailability of 32-40%, hence to optimize the oral bioavailability and absorption characeteristics buccal strips of diacerein have been formulated [6-8]

MATERIALS AND METHODS

Materials

Diacerein was obtained as a gift sample from IPCA Pharmaceuticals ltd. Dehradun. All other chemicals and reagents used were of analytical grade and quality.

Methods

Preparation of diacerein standard curve

Weighed 10 mg of DIACEREIN and dissolved in 10 ml of pH 6.8 phosphate buffer solution (1000 µg/ml). From this solution 1 ml was taken and diluted to 10 ml with PBS to get a solution containing 100 µg/ml. From this 1 ml was diluted to 10 ml to get working standard solutions of 10 µg/ml. This solution was scanned between 200-400 nm and an absorption maximum was determined and compared with literature value. Weighed 10 mg of DIACEREIN and dissolved in 10 ml of pH 6.8 phosphate buffer solution (1000 µg/ml). From this solution 0.5 ml, 1 ml, 2 ml, 3 ml, 4 ml was taken and diluted up to 100 ml using pH 6.8 phosphate buffer solution to obtain a working standard solution of 5- 40 µg/ml. The prepared concentrations were analyzed in UV-Visible spectroscopy at 258 nm.

Development of buccal strips

Mucoadhesive buccal patches of diacerein were prepared by solvent casting method. Various polymers were used based on their mucoadhesion strength and residence time. The following polymers were selected:

1. HPMC-K4M
2. Eudragit –RS-100
3. Sodium CMC
4. Sodium Alginate

Trial batches were prepared using these polymers alone and in combination in concentration ranging from 0.5% to 4%. Based on the results of trail batches a high concentration of 3% and a low concentration of 1% was optimized for buccal patches. each formulation contains 4% polymer concentration which was optimized based on the results of tensile strength, mucoadhesion residence time of trial batches. Diacerein buccal patches contain a mixture of HPMC-K4M/Eudragit RS 100 and Sodium Alginate/Sodium CMC

PROCEDURE

- The diacerein loaded strips for buccal drug delivery were prepared by solvent casting method using polymers different ratios.
- The polymeric solutions were prepared in double distilled water with constant stirring.

- The polymeric solutions were filtered through nylon gauze to remove debris and suspended particles. The resultant solution was left overnight at room temperature to ensure a clear, bubble-free solution. The solution was poured into a glass petri dish having 8 cm diameter.
- 50mg/sqcm equivalent of drug was added to each film. The backing membrane of ethyl cellulose was prepared for each of the films.
- Dried films were carefully removed, checked for any imperfections or air bubbles and cut into patches of 1sqcm in diameter by using fabricated punch (Table 1).

Table 1: Formulations chart.

Ingredients	DP1	DP2	DP3	DP4	DP5	DP6	DP7	DP8	DP9	DP10
Diacerein (mg)	50	50	50	50	50	50	50	50	50	50
HPMC	3%	2.50%	2%	1.50%	1%	-	-	-	-	-
Eudragit RS 100	1%	1.50%	2%	2.50%	3%	-	-	-	-	-
Sodium Alginate	-	-	-	-	-	3%	2.50%	2%	1.50%	1%
Sodium CMC	-	-	-	-	-	1%	1.50%	2%	2.50%	3%
Glycerine	2%	2%	2%	2%	2%	-	-	-	-	-
Propylene Glycol	-	-	-	-	-	2%	2%	2%	2%	2%
PVP K 100 (mg)	10	10	10	10	10	10	10	10	10	10
Solvent	q.s.	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of buccal patches

The prepared buccal strips were evaluated for parameters like physical appearance, thickness, weight variation, flatness, folding endurance, moisture uptake, moisture content, swelling study, drug content determination. *In-vitro* permeation and *ex-vivo* permeation using Franz diffusion cell and stability study of optimized formulations [9,10].

RESULTS AND DISCUSSION

The results are shown in Figures 1-11 and Tables 1-8.

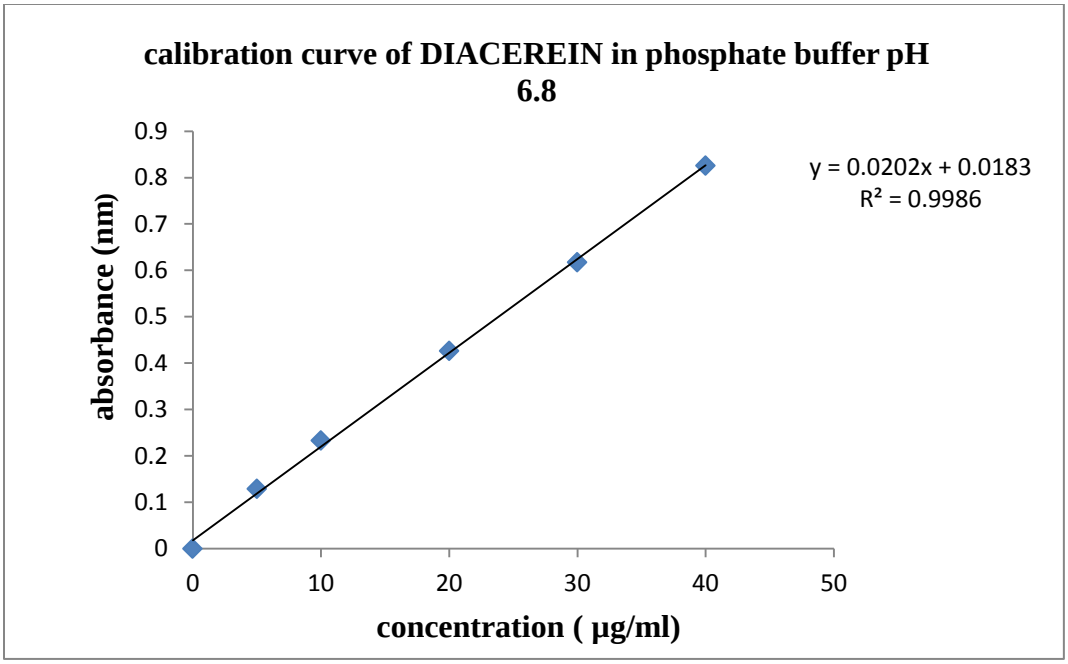

Figure 1: Calibration curve of diacerein.

Table 2: Diacerein buccal patches evaluation parameters.

Parameters	DP1	DP2	DP3	DP4	DP5	DP6	DP7	DP8	DP9	DP10
Surface pH	6.37 ± .1	6.32 ± 0.2	6.33 ± 0.4	6.37 ± 0.5	6.45 ± 0.1	6.75 ± 0.3	6.21 ± 0.4	6.54 ± 0.2	6.71 ± 0.2	6.67 ± 0.3
Thickness (Mm)	0.35 ± .002	0.34 ± .001	0.36 ± .004	0.37 ± .002	0.34 ± 0.04	0.33 ± 0.001	0.36 ± 0.003	0.37 ± 0.005	0.34 ± 0.005	0.33 ± 0.003
Folding Endurance	234 ± 4	238 ± 3	243 ± 2	219 ± 3	235 ± 1	267 ± 3	256 ± 4	274 ± 6	236 ± 5	248 ± 2
Weight Uniformity (mg)	99.5 ± .1	98.2 ± .05	98.3 ± .06	100.1 ± .03	97.9 ± .1	98.9 ± .09	98.6 ± .07	99.7 ± .06	99.5 ± .02	99.6 ± .03
Content Uniformity (%)	93.4 ± 0.12	94.5 ± 0.23	92.6 ± 0.43	96.5 ± 0.08	97.3 ± 0.021	97.3 ± 0.2	94.6 ± 0.34	95.7 ± 0.12	92.8 ± 0.51	94.6 ± 0.42
% Moisture Uptake	4.1 ± .1	3.4 ± .1	3.7 ± .3	3.8 ± .2	3.1 ± .2	3.9 ±	4.2 ± .3	4.3 ± .4	3.8 ± .1	3.7 ± .1
%Moisture Content	3.2 ± .04	2.1 ± .04	2.6 ± .02	2.7 ±	1.5 ± .01	1.7 ± .04	2.4 ± .03	2.7 ± .02	1.6 ± .03	1.5 ± .05
Vapour Transmission Rate	6.76 ± .3	2.56 ± .2	5.67 ± .1	4.5 ± .4	3.8 ± .5	5.8 ± .3	6.2 ± .2	7.1 ± .1	4.9 ± .3	5.1 ± .4
Mucoretention Time (Hours)	7.3 ± .3	7.6 ± .4	7.8 ± .3	7.9 ± .1	8.2 ± .1	8.3 ± .2	6.9 ± .2	7.1 ± .3	8.3 ± .1	8.1 ± .3
Mucoretention Strength (Gms)	24.56 ± .15	25.67 ± .23	24.34 ± .2	26.5 ± .14	25.78 ± .35	23.4 ± .26	25.3 ± .27	26.8 ± .13	27.8 ± .14	24.7 ± .17
% Swelling Index	63.4	65.3	68.2	67.5	69.3	71.2	62.3	64.5	62.3	67.8

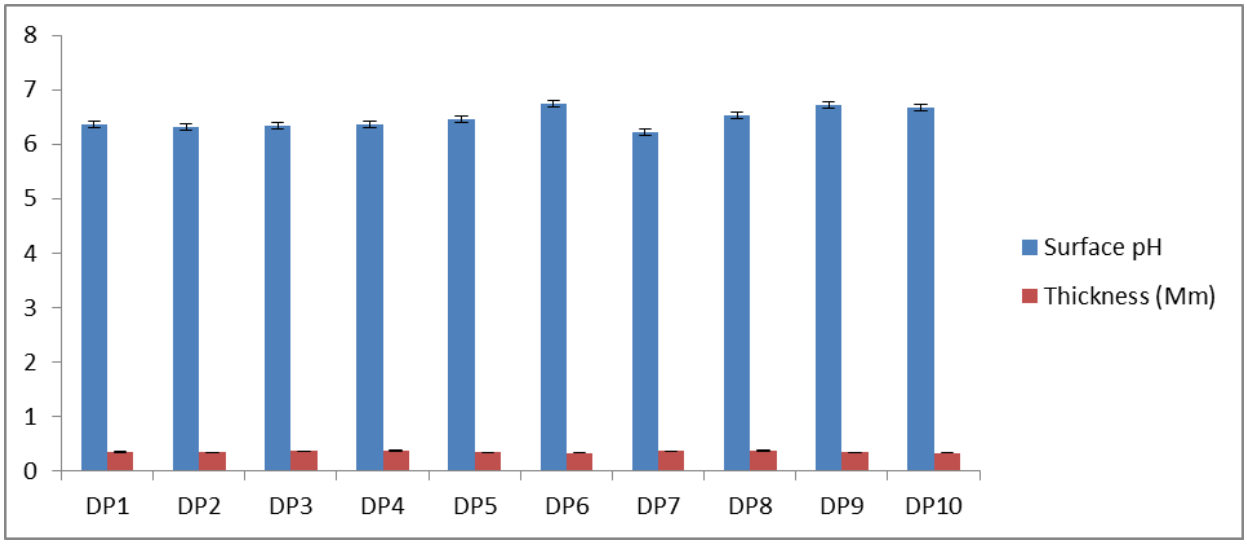

Figure 2: Surface PH and thickness of diacerein buccal patches.

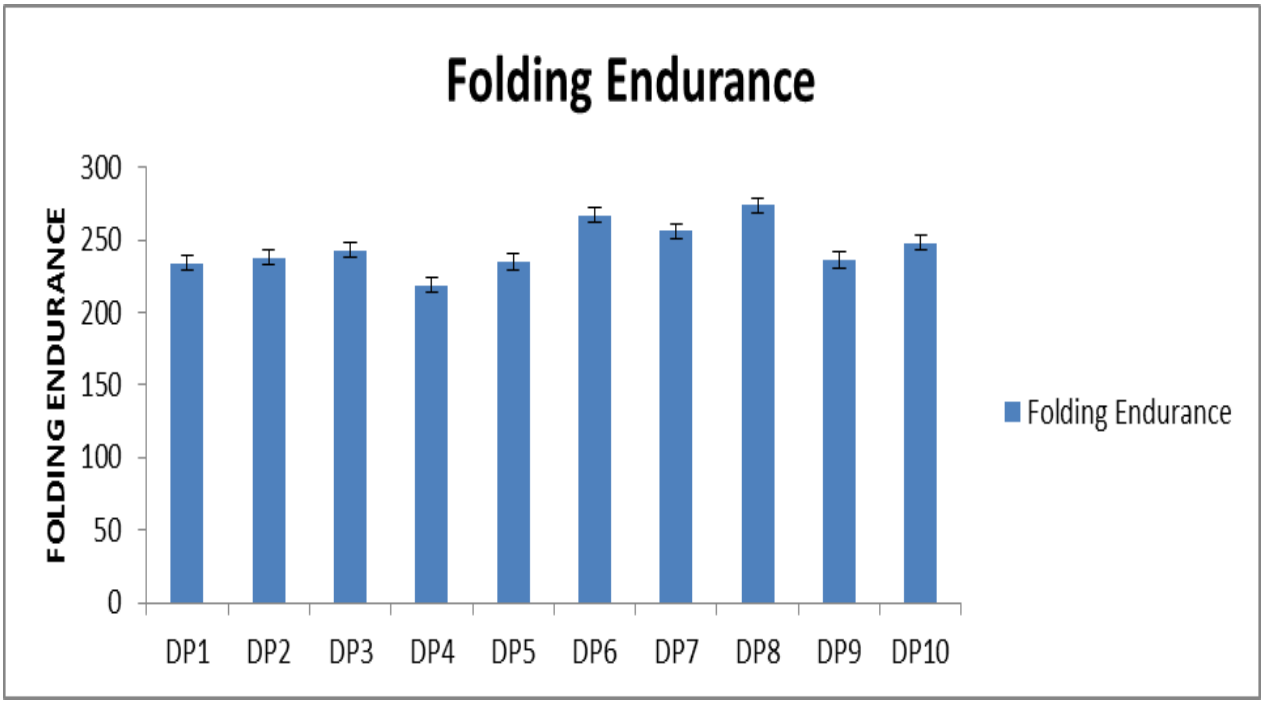

Figure 3: Folding endurance of diacerein buccal patches

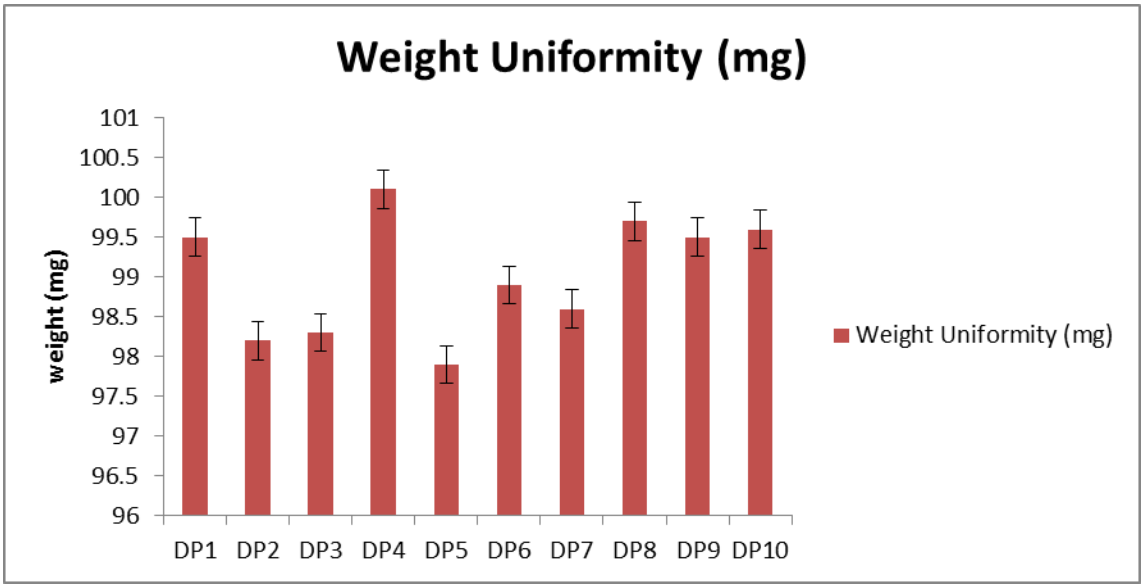

Figure 4: Weight variation of diacerein buccal patches.

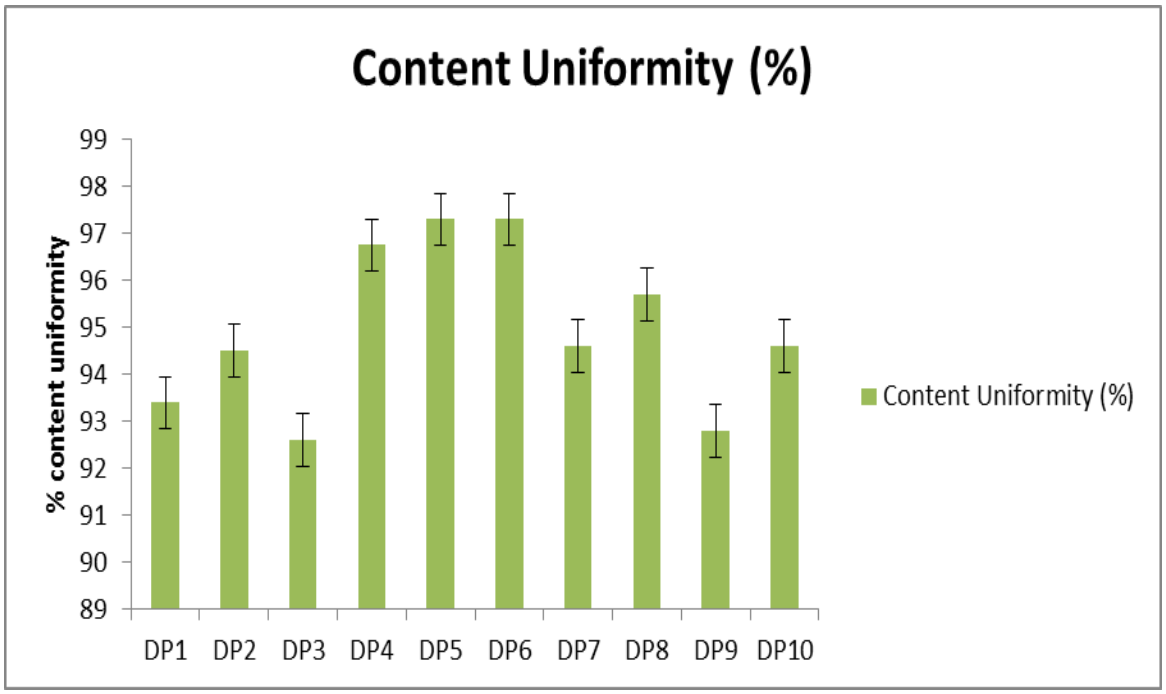

Figure 5: Content uniformity of diacerein buccal patches.

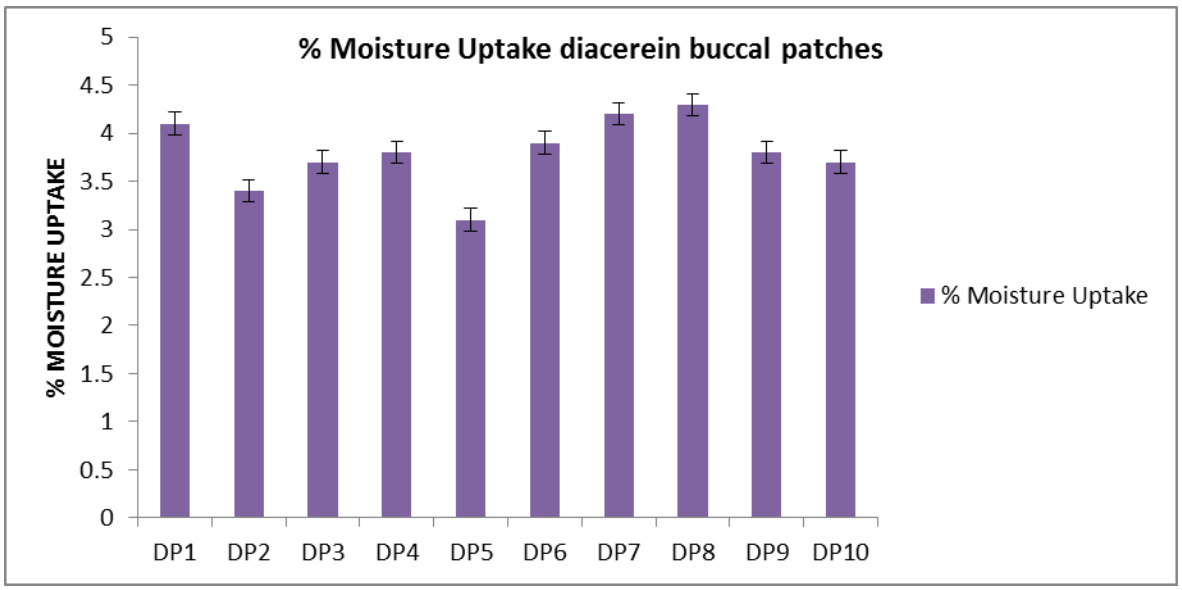

Figure 6: Moisture uptake of diacerein buccal patches.

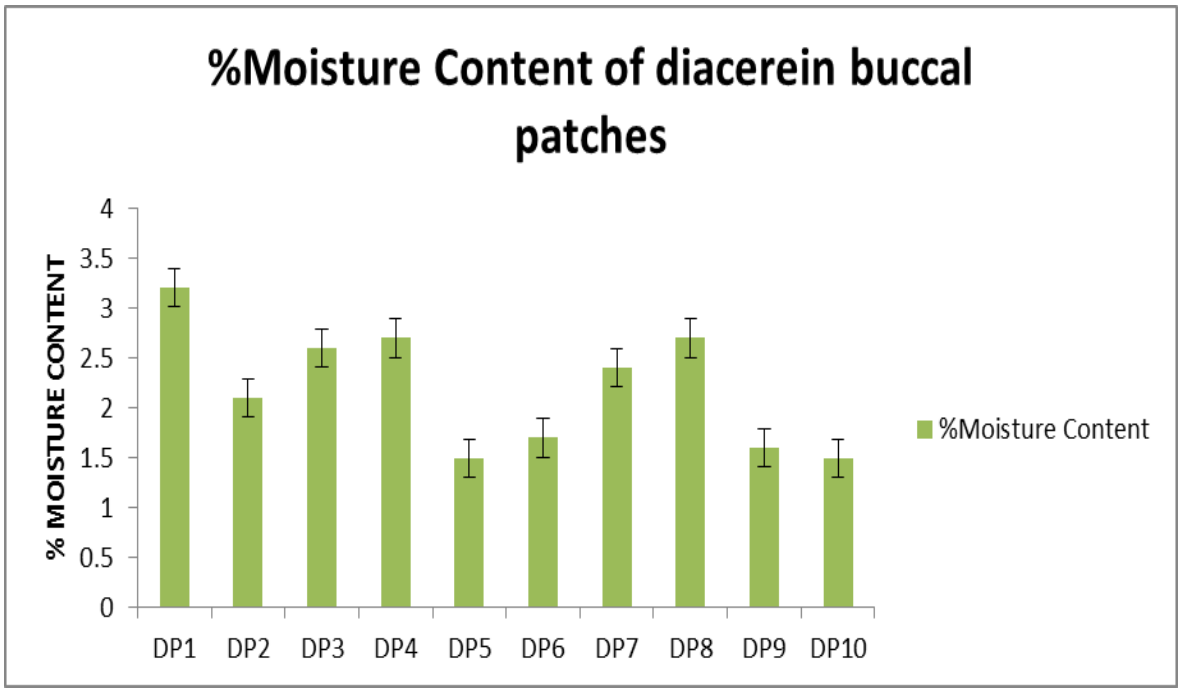

Figure 7: % Molisture content of diacerein buccal patches.

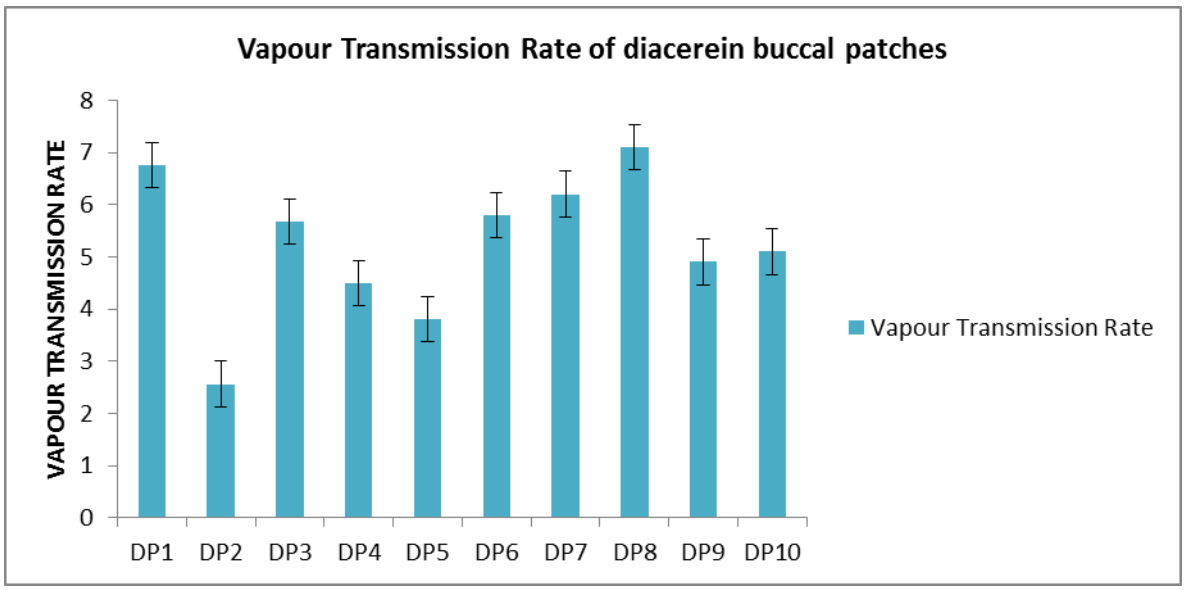

Figure 8: Vapour transmission rate of diacerein buccal patches.

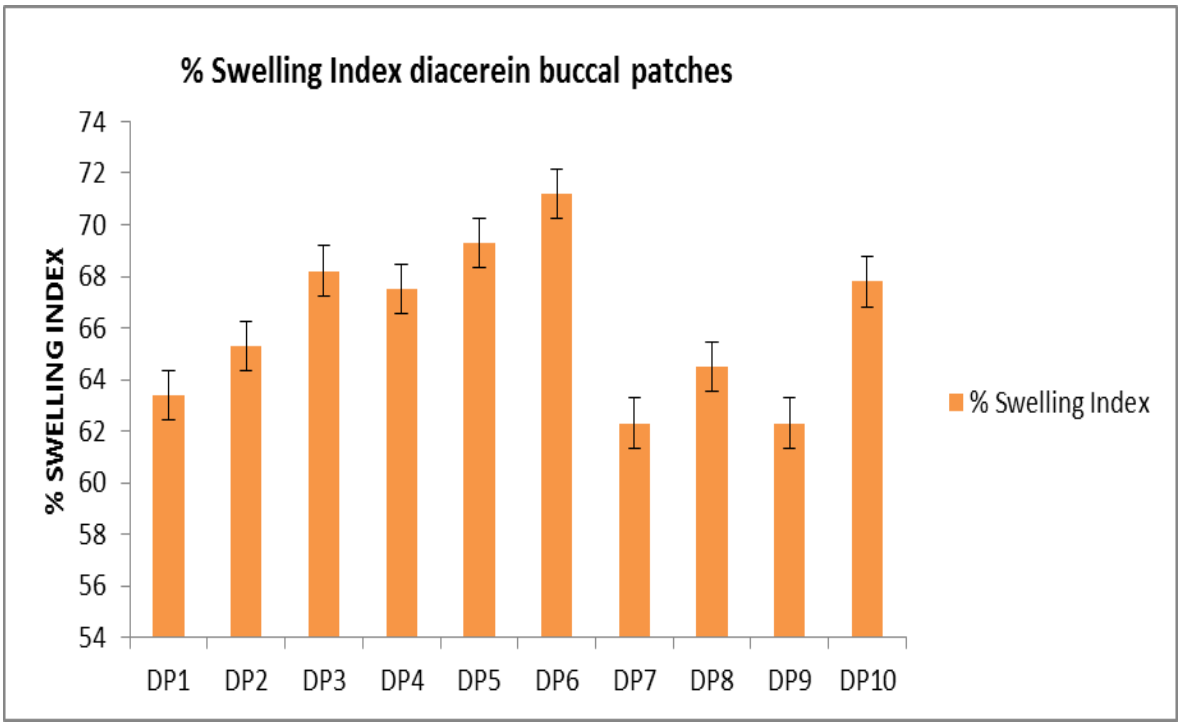

Figure 9: Swelling index of diacerein buccal patches

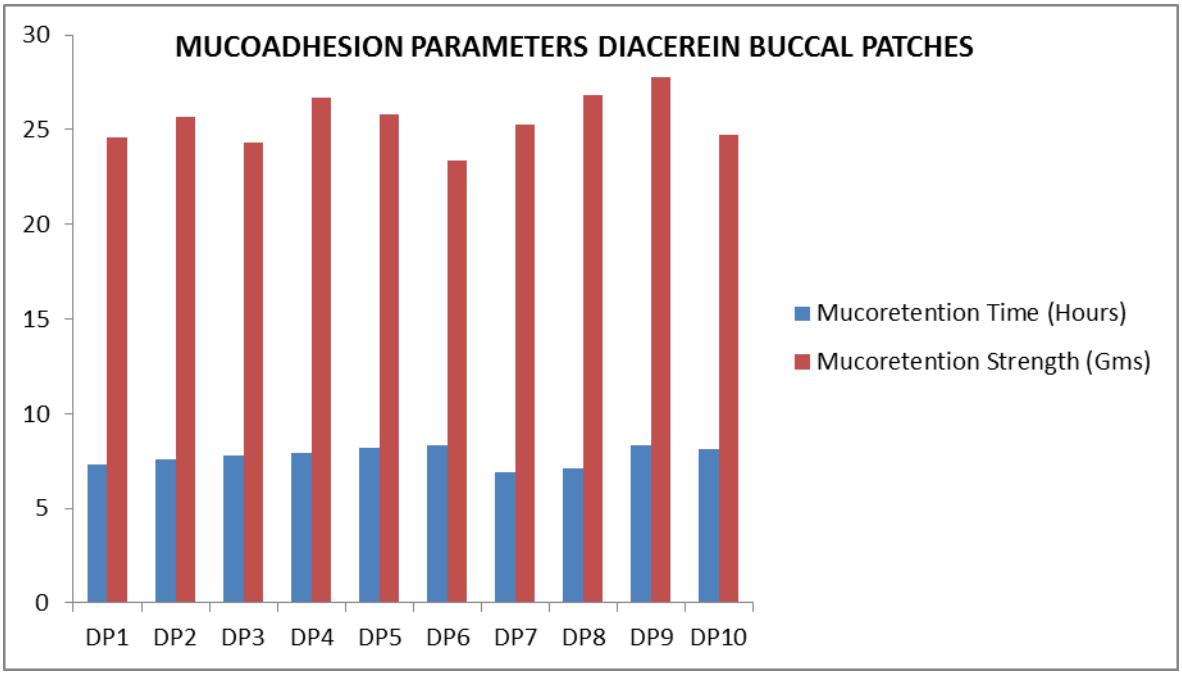

Figure 10: Mucoadhesion parameters of diacerein buccal patches.

Table 3: % *In-vitro* drug permeation study

Time vs. % Drug Release	DP1	DP2	DP3	DP4	DP5	DP6	DP7	DP8	DP9	DP10
1	2.2	1.7	1.9	3.4	4.1	2.8	1.3	2.3	2.6	2.8
2	5.1	4.3	2.9	6.5	8.4	5.7	3.1	4.8	6.7	6.2
3	9.7	9.6	5.7	12.6	12.4	11.7	6.5	8.7	13.5	14.6
4	18.5	21.3	11.2	19.1	18.7	19.4	12.4	15.7	19.6	21.3
5	26.4	27.6	16.8	25.3	25.1	26.9	18.1	21.4	28.1	29.7
6	38.7	33.4	26.7	32.1	35.4	35.7	27.4	27.8	35.6	37.6
7	47.6	39.6	35.6	39	45.2	43.2	36.5	36.7	41.5	43.4
8	54.3	45.6	42.3	46.2	51.3	51.7	45.3	45.1	47.5	51.2
9	62.4	52.3	48.7	53.1	55.6	59.6	52.3	54.3	56.4	59.8
10	69.7	58.7	56.4	59.8	61.8	67.5	58.7	60.2	60.4	64.5
11	74.5	64.6	65.7	67.5	67.5	73.2	68.9	68.2	64.5	68.1

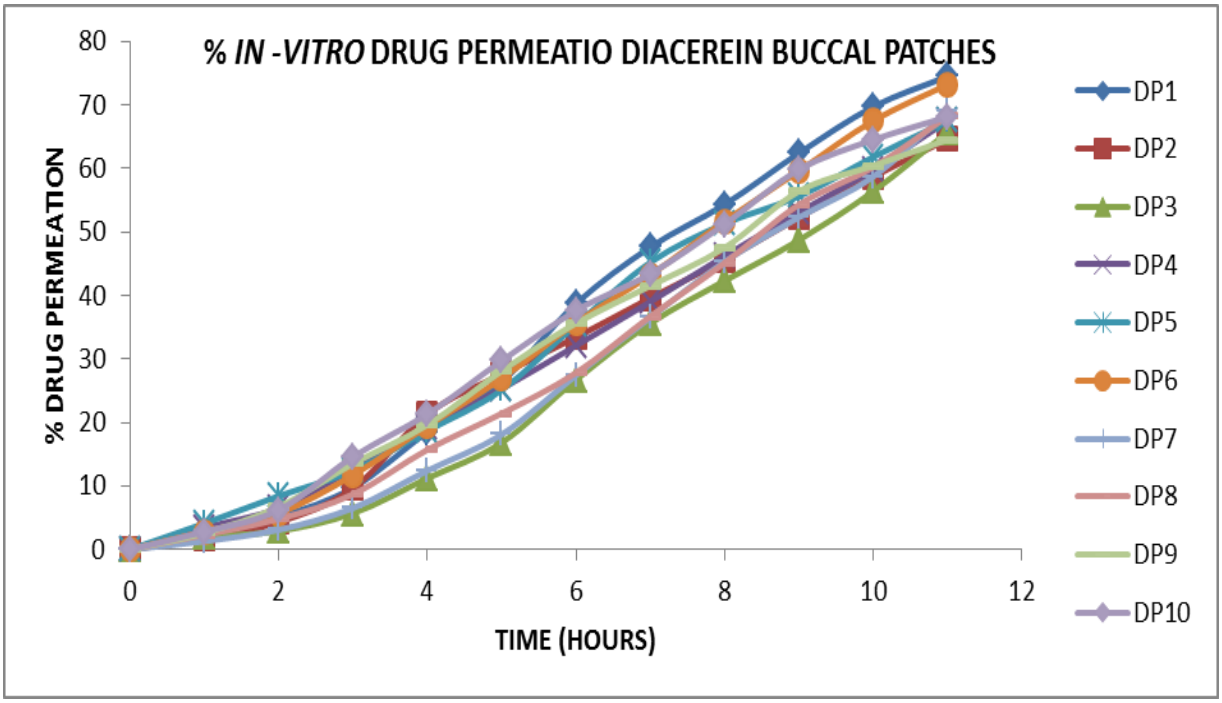

Figure 11: % *In-vitro* drug permeation of diacerein buccal patches.

Table 4: % *Ex-vivo* drug permeation of diacerein buccal patches.

Time	DP1	DP2	DP3	DP4	DP5	DP6	DP7	DP8	DP9	DP10
0	0	0	0	0	0	0	0	0	0	0
1	1.2	1.7	2.1	1.9	2.7	2.9	1.4	2.5	1.6	2.9
2	3.5	2.3	5.3	3.6	5.9	3.9	3.2	6.7	3.6	7.1
3	11.2	4.9	6.7	6.9	10.3	7.8	9.1	16.4	10.2	15.6
4	15.6	14.5	16.5	16.8	19.2	18.9	19.4	26.5	16.5	23.8
5	25.4	23.7	23.4	27.6	29.3	27.5	29.3	36.8	23.4	31.6
6	35.4	32.1	34.7	35.4	39.2	38.7	37.6	45.3	30	39.4
7	43.2	37.6	45.1	45.1	47.6	45.9	45.8	50.1	37.1	47.5
8	45.6	46.8	56.2	52.3	58.7	54.6	53.4	55.6	45.3	56.4
10	54.2	59.7	62.1	59.7	64.6	61.2	59	60.3	52.6	65.1
12	63.8	65.4	69.7	63.4	70.1	67.5	67.1	67.8	63.8	71.2

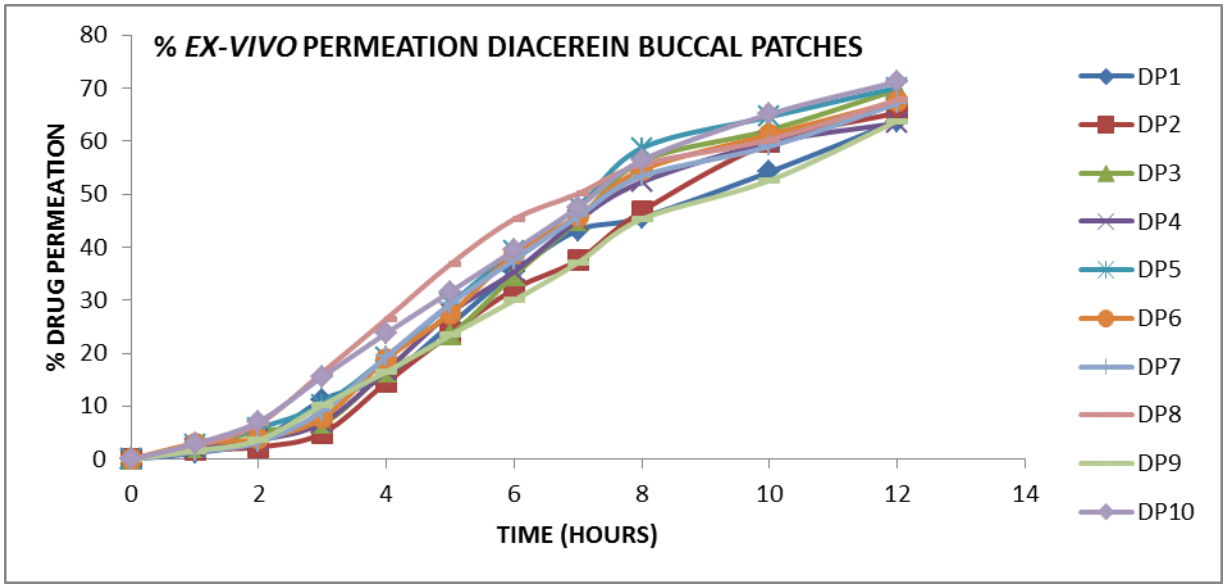

Figure 12: % *Ex vivo* drug permeation of diacerein buccal patches.

Table 5: Release kinetics of diacerein buccal patches (*In vitro* permeation).

R^2 value	DP1	DP2	DP3	DP4	DP5	DP6	DP7	DP8	DP9	DP10
Zero order	0.9824	**0.9899**	0.9633	0.9922	0.9879	0.9884	0.966	0.9764	0.9931	**0.9925**
First order	0.9472	0.9692	0.9162	0.9513	0.9645	0.9433	0.9136	0.9262	0.9747	0.9711
Higuchi matrix	0.9408	0.9385	0.9398	0.9292	0.9328	0.9346	0.938	0.9332	0.9342	0.9352
Peppas	0.9912	0.9819	0.9735	0.9962	0.9922	0.9943	0.9936	0.9942	0.9937	0.9902
Hix. Crow.	0.965	0.9806	0.9361	0.97	0.9762	0.9645	0.936	0.9474	0.9846	0.9828
Best fit model	Peppas korsmeyer	Zero order	Peppas korsmeyer	Peppas korsmeyer	Peppas korsmeyer	Peppas korsmeyer	Peppas korsmeyer	Peppas korsmeyer	Peppas korsmeyer	Zero order
Mechanism of release	Supercase II	Super case II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Super case II

Table 6: Release kinetics of diacerein buccal patches (*Ex-vivo* permeation).

R^2 value	DP1	DP2	DP3	DP4	DP5	DP6	DP7	DP8	DP9	DP10
Zero order	.9758	**.9709**	.9625	.9575	.9658	.9633	.9672	.9543	**.9874**	.9824
First order	.9753	.9550	.9523	.9633	.9647	.9678	.9743	**.9835**	.9689	.9808
Higuchi matrix	.9366	.9399	.9392	.9447	.9380	.9427	.9423	.9404	.9300	.9310
Peppas	.9719	.9492	**.9740**	.9637	**.9808**	.9508	.9657	.9588	.9826	.9835
Hix. Crow.	**.9793**	.9644	.9593	**.9640**	.9690	**.9699**	**.9758**	.9776	.9794	**.9868**
Best fit model	Hix. Crow.	Zero order	Peppas korsmeyer	Hix. Crow.	Peppas korsmeyer	Hix. Crow.	Hix. Crow.	First order	Zero order	Hix. Crow.
Mechanism of release	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II	Supercase II

Table 7: Stability study data: Effect on physical parameters [diacerein buccal patches].

Condition: 40°C, 75% rh

Parameters	DP2				DP10			
	0	**30**	**60**	**90**	**0**	**30**	**60**	**90**
Physical appearance	Smooth No bubbles Round shaped No physical deformations	Complies	Complies	Complies	Smooth No bubbles Round shaped No physical deformations	Complies	Complies	Complies
Surface pH	6.83 ± .03	6.82 ± .02	6.83 ± .01	6.83 ± .01	6.75 ± .02	6.72 ± .02	6.72 ± .01	6.74 ± .03

Table 8: Stability study data: Effect on physical parameters [diacerein buccal patches].

Condition: 25°C, 60% RH.

Parameters	**DP2**				**DP10**			
	0	**30**	**60**	**90**	**0**	**30**	**60**	**90**
Physical appearance	Smooth No bubbles Round shaped No physical deformations	Complies	Complies	Complies	Smooth No bubbles Round shaped No physical deformations	Complies	Complies	Complies
Surface PH	6.93 ± .02	6.92 ± .02	6.93 ± .01	6.91 ± .02	6.57 ± .02	6.56 ± .02	6.52 ± .02	6.544 ± .03

DISCUSSION

Standard curve of diacerein was prepared in pH 6.8 phosphate buffer; a linear curve was obtained with range 5-40 µg/ ml and Coefficient of correlation 0.998. Ten batches of buccal strips were formulated by varying the polymer amounts between 1 to 3% and total amount of polymer being 4%. The prepared strips were found to be elegant in appearance, bubble free, stable and free form any physical deformations. The prepared formulations were evaluated for various evaluation parameters and the results were analyzed, optimized. The formulations showed surface pH in the range of 6.2 to 6.8 showing no irritation to the oral buccal mucosa, content uniformity was found to be in the range 92% to 97%, muco-adhesive strength was in the range of 24 g to 28 g while mucoadhesive retention time was within 6.5 to 8.2 hours. All other parameters were found to be within the optimum limits without any significant differences. The formulations were subjected to in-vitro and ex-vivo permeation studies in which they showed optimum controlled release of upto 75% in 10 hours. Release kinetics was applied to all formulations showing the best fit models and release mechanisms. On the basis of release mechanisms two formulations (DP2 and DP10) were selected to be the best or optimum and stability study was performed on these formulations. The results of stability study were found to be satisfactory with the tested parameters being within limits.

CONCLUSION

Ten batches were prepared of diacerein loaded buccal strips using four polymers viz HPMC, Sodium CMC, Sodium alginate and eudragit. All the formulations were found to be stable, elegant in physical appearance and without any physical deformations.

The formulations showed optimum results when tested for various physical parameters and also faired optimally in release kinetics and stability studies. The optimized formulations DP and DP were by far the best amongst all the batches. The release kinetics suggest swelling based erosion mechanism and many of the formulations show zero order controlled release along with peppas korsmeyer mechanism. The formulations were found to be stable under accelerated conditions when tested for three months suggesting the optimization of the formula which can be used of the development of other buccal formulations as well. The formulation have also showed good correlation between in-vitro and ex vivo permeation studies. The formulations can be further subjected for in-vivo characterization and long term stability studies.

REFERENCES

1. Çelik, B., Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. *Drug Design Development and Therapy*, 2017, 11, 3355-3365.
2. Pathan, Asif, and Dev, Asish, Formulation and evaluation of bioadhesive drug delivery System. *Pharmaceutical and Biological Evaluations*, **2016.** 3(3): 377-387.
3. Yogananda, R ., et al. Formulation and evaluation of mucoadhesive buccal patches of Tramadol hydrochloride. *Am. J. Pharmtech Res*. **2012.** 2(2).
4. Pokhariyal et al., Drug delivery via the buccal patch – A novel approach. *Indo American Journal of Pharm Research*, **2013.** 3(2).
5. Raghavendra Rao, NG., Formulation and evaluation of mucoadhesive buccal bilayered tablets of salbutamol. *Int. J. Drug Dev. & Res*, 2012. 4(4): 375-384.
6. Verma, S., An overview on buccal drug delivery system. *Int J Pharm Sci*, **2011.** 2(6): 1303-21.
7. Rao, MBM., et al. *Int J Pharm and Pharm Sci*. **2011.** 2(6): 85-90.
8. Khairnar, GA., and Sayyad, FJ., Development of buccal drug delivery systembased on mucoadhesive polymers. *Int J Pharm Tech*, **2010.** 2(1): 719-735.
9. Das, R., et al. *Int J Pharma Sci*. **2011.** 6(1): 64-115.
10. Smart, SJD., The basics and underlying mechanisms of mucoadhesion. *Adv Drug Deliv Rev*. **2005.** 57(11): 1556-1568.