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Development and in vitro evaluation of polyphenols (catechin) loaded mucoadhesive buccal patches

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ABSTRACT

The buccal mucoadhesive patches of catechin were fabricated with objective of avoiding first pass metabolism and prolonging duration of action. The mucoadhesive polymers used in formulations were Hydroxyl propyl methyl cellulose (HPMC E15), carboxy methyl cellulose (CMC), chitosan and *Vinga radiata* extract. These formulations were characterized for physiochemical parameters, in vitro retention time, in vitro bioadhesive strength, percent hydration, and drug release. The modified in vitro assembly was used to measure the bioadhesive strength of patches with fresh goat buccal mucosa as a model tissue. The best mucoadhesive performance and in vitro drug release profile were exhibited by the patches contains chitoson and VR (*vinga radiata* extract) in the ratio of 1:1.5. This formulation was more comfortable to the user due to less erosion, faster hydration rate, and optimum pH of surrounding medium.

Keywords: Buccal mucoadhesive patches, *Vinga Radiata* extract, Bioadhesive Strength, *In vitro* retention time, catechin.

INTRODUCTION

The catechin has a half-life of 1 hrs and shows a bioavailability of less than 5 percentages. The catechin has low bioavailability and high first pass metabolism, the buccal release formulation has its own significance for improving the systemic concentration.[1] The polymers used in this investigation are chitosan, HPMC and CMC. Chitosan is a natural bio compatible and bio degradable polymer, extensively used in the development of mucoadhesive buccal drug delivery. Chitosan as a biodegradable polymer has proved its ability as the safest and efficient material for the development of novel drug delivery system for various drug molecules. Due to its inherent properties this is one of the preferred polymers for the formulation developers. Chitosan has an excellent film forming ability and better mucoadhesive property. the mucoadhesive property of chitosan either due to its ability to form secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged mucin. Apart from this chitosan has a cell binding and membrane permeation activity. So in this investigation, an attempt has been made to develop mucoadhesive buccal patches of Catechin by using chitosan, thus expecting a modified release characteristics of the drug.[2,3]

MATERIALS AND METHODS

Catechin, HPMC, CMC was obtained as a gift sample from KTPL, Chennai , chitosan was obtained from Balaji chemicals, Gujarat. All other reagents and chemicals were of analytical or pharmaceutical grade.

Extraction of Saponin from *Vinga Radiata*

Dried *Vinga radiata* seed were homogenized with distilled water, refluxed for 4 hours. Then concentrated in rotary evaporated. Extracted with 1-butanol, which was previously saturated with water. This 1- butanol fraction dried in rotary evaporated and residue dissolved in methanol. Saponins were precipitated by three time volume of ethyl acetate, and centrifuged for 15 minutes at 5000 rpm. Supernatant discarded and residue dried in vacuum dryer, stored in well closed container. Saponins were detected by TLC method. Using Kieselgel 60 F-254 plate, with chloroform-methanol-water (65:35:10 v/v). The components were visualized by heating at 105^{o}C.

Preparation of Buccal Patches of catechin with *Viga Radiata* Saponine

Buccal mucoadhesive films were prepared using polymer or polymer blends along with the drug and a suitable solvent. The buccal mucoadhesive films of polyphenols were prepared using sodium carboxyl methyl cellulose and Hydroxyl propyl methyl cellulose E15 cps polymers by casting method. HPMC polymer (1000 mg), *Vinga radiata* saponin, Poly ethylene glycol (PEG 600) and sodium CMC was weighed accurately and placed in 5 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 15 minutes for swelling of polymer. Further 3 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then 1ml of MDC was added to the polymer solution. The drug (polyphenol) solution was added to the polymer dispersion. The whole mixture was mixed thoroughly with the help of a magnetic stirrer, Finally 1 ml of distilled water added and stirred well. The glass mould of size 5 × 3 cm^2 was placed over a flat surface. The drug-polymer mixture was poured into the glass mould. The mould was kept in hot air oven for 1 hour at 50^{o}C for drying and sudden evaporation. After this period, an inverted funnel was placed over the mould overnight to remove the remaining solvent. The film was removed from the mould, packed in wax paper, and stored in a desiccator.

Preparation of standard curve of polyphenols

Aliquots of 0.1% gallic acid stock solution containing 20-200µl of gallic acid were dispensed into triplicate sets of 25 ml volumetric flasks. 500 µl of Folin Ciocalteau (diluted 1:1 with water) reagent followed by 100µl of 30% Na2CO3 were added to the flasks and mixed. The volume is made upto 25 ml mark by distilled water and allowed to react at room temperature for 30 min. The blue color developed is read against reagent blank at 730 nm in a Shimadzu UV-VIS (UV-2450) spectrophotometer. The gallic acid concentration was plotted against absorbance.

Folding Endurance[4,5]

Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Patch thickness[6]

The thickness of the buccal patch was measured by using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Weight variation

Ten patches of 1cm^2 were weighed individually and average of those patches measured.

Surface pH [7,8,9]

Buccal patches were left to swell for 1 hour on the surface of 2% agar plate, it was allowed to stand until it is solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

Percentage swelling

After determination of the original patch weight and diameter, the samples were allowed to swell on the surface of Petridis kept in an incubator maintained at

37 ± 0.2^0C. Increase in the weight of the patch (n=3) was determined at pre-set time intervals (1-5h). The percentage swelling of the patches was calculated using the formula % S = (Xt – X0/X0) x 100, where Xt is the weight of swollen patch after time t, X0 is the initial patch weight at zero time. (7)

% Moisture content[4,5]

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the patches were taken out and weighed. The moisture content (%) was determined by the formula:

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Bioadhesive Strength[12, 13]

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance.

Instrument

The apparatus was locally assembled and was a modification of the apparatus applied by Parodi et al. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane.

Method

The fabricated balance described above was used for the bioadhesion studies. The bovine cheek pouch, excised and washed was fixed to the movable platform. The mucoadhesive patch was fixed of 3 cm², was fixed to the stainless steel lamina using 'feviquick' as adhesive. The exposed patch surface was moistened with 1 ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into the contact with the mucosal surface. A preload of 20 g was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosal membrane. The weight required to detach the patch from the mucosa give the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before taking reading.(8)

%Drug content[14,15,16]

Prepared buccal patch was dissolved in 100ml of Phosphate buffer solution (PBS) of pH 6.8 using a magnetic stirrer for 12 hours and then sonicated for 30 minutes. The solution was centrifuged and then filtered. The drug content determination was done by using UV spectroscopy at 223 nm.

In vitro diffusion study[17.18]

In vitro diffusion study was performed by using modified franz diffusion cell across cellophane membrane. Phosphate buffer solution (PBS) of pH 6.8 was used as medium for diffusion study. Patches of dimension $2x2cm^2$ were placed on the membrane, which was placed between donor and receptor compartment of franz diffusion cell. Cellophane membrane was brought in contact with PBS of pH 6.8 filled in receptor compartment. Temperature was maintained at 37^0C with stirring at 50 rpm using magnetic bead stirrer. 1ml of sample was withdrawn from receptor compartment at pre-determined interval and was replaced with fresh PBS of pH 6.8. With suitable dilution, samples were measured for absorbance at 730 nm using UV visible spectrophotometer. Using 20-200µl of gallic acid as standard was dispensed into triplicate sets of 25ml volumetric flasks. 500µl of Folin Ciocalteau (diluted 1:1 with water) reagent followed by 100µl of 30% Na2CO3 were added to the flasks and mixed. The volume is made upto 25 ml mark by distilled water and allowed to react at room temperature for 30 min. The blue color developed is read against reagent blank at 730 nm in a Shimadzu UV-VIS (UV-2450) spectrophotometer. The gallic acid concentration was plotted against absorbance.

Stability study[19,20]

Stability studies were performed in accordance with ICH guidelines for accelerated stability testing. Patches ($2x2$ cm^2) were wrapped individually in

aluminum foil and maintained at refrigerated temperature (4±2^{0}C), room temperature (30±2^{0}C), and oven temperature (45^{o}C and 75 % RH) for a period of 1 month. Changes in the appearance and drug content of the stored patches were investigated after storage period.

RESULTS AND DISCUSSION

The results of evaluations were summarized in table (Table No.2). The developed catechin patches were smooth and flexible. All the characteristics such as folding endurance, thickness average weight, % swelling index, moisture content, tensile strength and % drug content were increased with increase in concentration. The reason behind this is, at higher concentration the more polymer chain with flexible nature may be available, which resulted in higher folding endurance value[22]. It was already proved by the researchers that, the thickness, average weight, % swelling index, moisture content and tensile strength will increases with increase in concentration of polymer[23,24]. The surface pH value indicating that the patches may not produce any irritation to oral mucosa and safer for application[25]. The % drug content was higher with VR-2, this may be due to higher entrapment efficacy of chitosan polymer at higher concentration[24].

The diffusion data obtained for the buccal patches containing catechin with different concentrations of chitosan and VR extract were closely assessed. The % drug diffused was plotted against time (Table No.3 and Fig No.1). The % drug diffused from formulation VR-1 and VR-2 were found to be 61.40% and 66.226% respectively after 6 hours diffusion (Table No.3). From the data it can be assumed that the %drug diffused from formulation VR2 containing VR extract and chitosan had approximately 1.5% greater release than formulation plain patches (not shown in table). When VR extract combines with the optimum level of polymer, there may be a possibility of good initial burst release as well as better diffusion profile for a drug such as catechin. This may be a possibility for improved release profile of formulation VR2. Apart from this, chitosan possess inherent permeation enhancing property, which might have resulted in a synergistic effect with VR extract incorporated in formulation for improved release properties of chitosan based buccal patch[26]. After good initial burst release from F2, good controlled release profile was maintained for the entire duration of investigation. This may be due to the natural polymeric structure of chitosan which might have been reflected in VR2 with 1% chitosan.

Accelerated stability studies were performed in accordance with ICH guidelines with necessary modifications. The studies were carried out to verify the changes in physical characteristics such as color, thickness, folding endurance and pH along with changes in % drug content at three different conditions of higher temperature (45±2^{0}C), room temperature (30±2^{0}C), and refrigeration temperature (4±2^{0}C). After the completion of one month, formulation VR1 with 1% chitosan had 98.90±0.05% of drug content reported at room temperature, with a minor decrease during the storage at refrigeration temperature of 4 ± 2^0 C. But when the drug content was estimated for VR2 at oven temperature, the drug content was 97.30±0.05%. Similar drop in %drug content were observed in case of formulation VR2 when kept at higher temperature. Loss in % drug content was found to be minimum in case of formulation of VR2.

Table 1: COMPOSITION OF FORMULATIONS

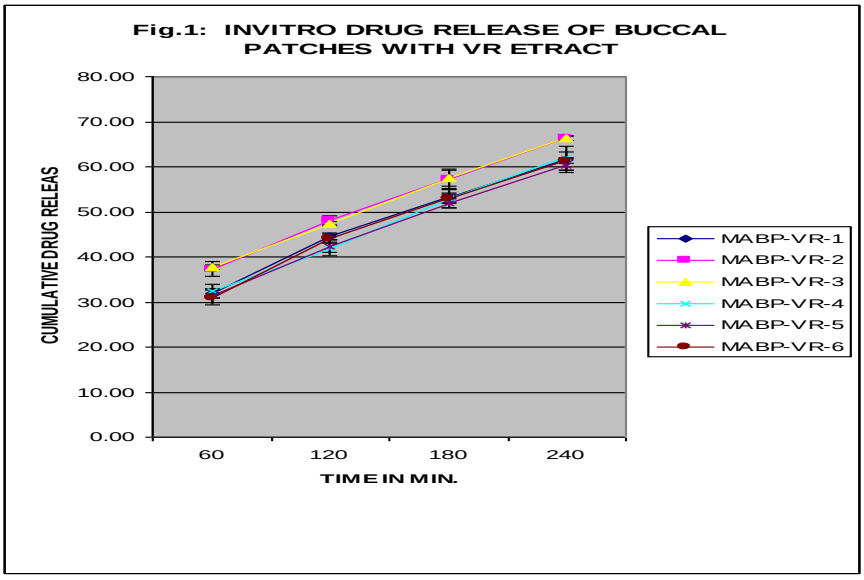
	HPMC (mg)	SCMC (mg)	Chitosan (mg)	PEG 600 (mg)	VR (mg)
MABP-VR-1	700	200	10	50	5
MABP-VR-2	700	200	10	75	10
MABP-VR-3	700	200	10	100	15
MABP-VR-4	700	200	10	125	20
MABP-VR-5	700	200	10	150	25
MABP-VR-6	700	200	10	175	30

Table 2: CHARACTERIZATION OF DEVELOPED FORMULATIONS

FORMULATION CODE	VR-1	VR-2	VR-3	VR-4	VR-5	VR-6
Appearance	smooth	Smooth	Smooth	Smooth	Smooth	smooth
Texture	Flexible	Flexible	Flexible	Flexible	Less Flexible	Less Flexible
Folding endurance	290±2	280±2	2880±2	260±2	240±2	200±2
Thickness(mm)	5±0.1	5.6±0.1	6.1±0.1	6±0.1	6.3±0.1	6.6±0.2
Surface pH	6.6	6.8	6.6	6.7	6.5	6.7
Swelling index(after 5 hours)	30	33	32	31	30	30
% Moisture content	1.4	1.6	1.5	1.7	1.6	1.8
Bioadhesive strength (Kg/m/sec)	121	196	177	140	177	149
% Drug content	96.05	97.9	95	98.3	96.5	98.79

Table:- 3 *IN VITRO* DRUG RELEASE OF BUCCAL PATCHES WITH VR EXTRACT

S.NO		Cumulative Drug released %			
		60 min	120 min	180 min	240 min
1	MABP-VR-1	31.83	44.54	53.08	61.40
2	MABP-VR-2	37.33	48.00	57.33	66.22
3	MABP-VR-3	37.67	47.23	57.47	60.42
4	MABP-VR-4	32.33	41.67	53.00	58.00
5	MABP-VR-5	31.33	42.40	52.00	60.33
6	MABP-VR-6	31.00	44.00	53.00	61.33



CONCLUSION

This investigation established the effectiveness of chitosan as a polymer to develop buccal patches containing catechin. The results shown that buccal patches developed using chitosan were showing excellent characteristics which was ideally required for buccal patches,. More or less the patches were

stable at varying conditions. In vitro diffusion profile of catechin from chitosan was showing good initial burst release along with excellent controlled release profile for 6 hours duration. Based on investigation results, it may be suggested that 1.5 % is the optimum concentration to develop a good buccal patch containing catechin. Design and development of such buccal patches may be highly beneficial which can deliver drug up to a period of 12hrs duration. Hence application of buccal may ensure sufficient level of Catechin in the body to produce the possible antioxidant effect.

REFERENCES

[1] Sarathchandran C and Shijith KV. A concise insight on mucoadhesive buccal drug delivery system. Lamb Acad Pub. 2012:1-65.
[2] KV. Shijith, Sarath Chandran C, Vipin KV, Ann Rose Augusty and Premaletha K. A review on basics behind development of muco adhesive buccal drug delivery systems. IJAPBC. 2013;2(2):310-317.
[3] Roy S, Pal K, Anis A, Pramanik K and Prabhakar B. Polymers in mucoadhesive drug delivery system, A brief note. Designed monomers and polymers. 2009;12:483- 495.
[4] Indira Muzib Y and Srujana Kumari K. Mucoadhesive buccal films of glibenclamide: Development and evaluation. Int J Pharma Ivn. 2011;1(1):42-47.
[5] Vinod R, Ashok kumar P, Someswara Rao B, Suresh V. kulkarni and Shankar MS. Design and evaluation of miconazole nitrate buccal mucoadhesive patches. J Pharmacy Res. 2010;3(6):1338-1341.
[6] Khairnar GA and Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymers. Int J PharmTech Res. 2010;2(1):719-735.
[7] Jain NK. Controlled and novel drug delivery, CBS Publishers and Distributors, 1st Edition.2010:52-81.
[8] Raghavendra Rao NG and Suryakar VB. Formulation and evaluation of montelukast sodium mucoadhesive buccal patches for chronic asthma attacks. Int J Pharma and Bio Sci. 2010;1(2).
[9] Balamurugan M, Saravanan VS, Ganesh P, Senthil SP, Hemalatha PV and Sudhir Pandya. Development and In-vitro Evaluation of Mucoadhesive Buccal Patches of Domperidone. Res J Pharmacy and Tech. 2008;1(4).
[10] Semalty A, Mona Semalty and Nautiyal U. Formulation and evaluation of mucoadhesivebuccal films of Enalapril maleate. Ind J Pharma Sci. 2010;72(5):571– 575.
[11] Nappinnai M, Chandanbala R and Balajirajan R. Formulation and evaluation of nitrendipine buccal films. Ind J Pharm Sci. 2008;70(5):631-635.
[12] Wong CF, Yuen KH and Peh KK. Formulation and evaluation of controlled release Eudragit buccal pathces. Int J Pharm. 1999;178(1):11-22.
[13] Balamurugan K, Pandit JK, Choudary PK and Balasubramaniam J. Systemic absorption of Propranolol Hydrochloride from buccoadhesive films. Ind J Pharm Sci. 2001;63(6):473-480.
[14] Nafee NA, Ismail FA, Boraie NA and Mortada LM. Mucoadhesive buccal patches of Miconazole nitrate: in vitro/in vivo performance and effect of ageing. Int J Pharm. 2003;264(1-2):1-14.
[15] Panigrahi L, Pattnaik S and Ghosal SK. Design and characterization of mucoadhesive buccal of Diclofenac Sodium. Ind J Pharm Sci. 2005;67(3):319-326.
[16] Pavankumar GV, Ramakrishna V, William GJ and Konde A. Formulation and evaluation of buccal films of Salbutamol Sulphate. Ind J Pharm Sci. 2005;67(2):160-164.
[17] Chinna Reddy Palem, Ramesh Gannu, Vamshi Vishnu Yamsani, Shravan Kumar Yamsani and Madhusudan Rao Yamsani. Development of bilayered mucoadhesive patches for buccal delivery of felodipine: in vitro and ex vivo characterization. Cur trends in Biotech and Pharmacy. 2010;4(2).
[18] Thimmasetty J, Pandey GS and SatheshBabu PS. Design and evaluation of carvidilol buccal mucoadhesive patches. Pak J Pharm Sci. 200;21(3):241-248.
[19] Garry Kerch and Vadim Korkhov. Effect of storage time and temperature on structure, mechanical and barrier properties of chitosan-based films. Euro Food Res and Tech. 2012;232(1):17-22.

[20] Kristine Romøren, Astrid Aaberge, Gro Smistad, Beate J Thu and Oystein Evensen, Long-term stability of chitosan-based polyplexes, PubMed- Pharm. Res.2005;21(12):2340-2346

[21] Punitha S, Girish Y, Polymers in mucoadhesive buccal drug delivery system – A review. Int J Res Pharm Sci. 2010;1(2):170-186.

[22] Wong CF, Yuen KH and Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm. 1999;178(1):11-22.

[23] Inampudi Ajit, Adimoolan Senthil, Bhosale Rahul and NarayanaSwamy VB. Formulation and evaluation of Velnafaxine HCl buccal patches. Int Res J of Pharmacy. 2012;3(1):226-231.

[24] Ram Chand Dhakar, Sheo Datta Maurya, Bh.anu PS Sagar, Sonia Bhagat, Sunil Kumar Prajapati and Chand Prakash Jain. Variables influencing the drug entrapment efficiency of Microspheres: A Pharmaceutical Review. Scholars Research Library. 2010;2(5):102-116.

[25] Liji Jacob CI and Sajeeth K. Santhi. Design, Development and Evaluation of the Mucoadhesive s of CATECHIN for Buccal Delivery. Int J of Pharmacy and Techn. 2012;4(1):3883-3900.

[26] Muralikrishna K, Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Himabindu S and Shravankumar Yamsani. Comprehensive review on buccal delivery. Int J Pharm. 2012;2(1):205-217.