INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

FORMULATION AND EVALUATION OF BUCCAL PATCHES OF CARVEDILOL PHOSPHATE

Sreekanth M.C [1]*, Anusha Ajayakumar [2], K. Santhi [3]
[1]Assistant Professor, Department of Pharmaceutics Nehru College of Pharmacy, Pampady, Thrissur, India
[2]Assistant Professor, Department of Pharmaceutical Analysis, Nehru College of Pharmacy, Pampady, Thrissur, India
[3]Professor, Department of Pharmaceutics, JSS College of Pharmacy, Mysoore, India
*Corresponding Author Email: sreekanthmc85@gmail.com

Article Received on: 10/06/16 Revised on: 15/07/16 Approved for publication: 11/08/16

DOI: 10.7897/2230-8407.07892

ABSTRACT

Carvedilol is a non-selective adrenergic antagonist with no intrinsic sympathomimetic activity widely used to treat essential hypertension and angina pectoris. Although it is completely absorbed from the gastrointestinal tract, the systemic availability is approximately 25-35% because of high first-pass metabolism. The aim of the present study was to develop the mucoadhesive buccal patches of carvedilol phosphate and to evaluate *in vitro* performance of buccal patches of carvedilol by using Chitosan, PVP K 30, PVP K 90, HPMC, and propylene glycol as plasticizer. IR spectra of carvedilol along with polymers indicated no interaction between carvedilol and all the four selected polymers. After optimizing the formula from the three combinations of polymeric patches, three formulas were selected for drug loading, respectively from each combination they were loaded with 30mg (D_1), 40mg (D_2), 50mg (D_3) and 60mg (D_4) carvedilol phosphate. The *in vitro* studies shows that there was an increase in the extend of duration of drug release with increase in concentration of chitosan in the formula. Kinetic of release of drug from all the drug loaded batches were found to follow first order. The formulated buccal patches of carvedilol phosphate was found to be suitable buccal delivery system to avoid the first pass metabolism of carvedilol phosphate which will have other added benefits like longer duration of action and quicker onset of action as compared to tablets of carvedilol phosphate.

Keywords: Carvedilol phosphate, mucoadhesive buccal patch.

INTRODUCTION

The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enterable methods.

Transmucosal delivery of therapeutic agents is a popular method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. This efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body's natural defence mechanisms.

Various mucoadhesive formulations were suggested for buccal delivery that includes buccal patches, adhesive tablets and adhesive gel. Buccal patches overcome some of the drawbacks of other dosage forms. They have unique characteristics including flexibility, relative rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. The patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter and intra-individual variability.

Transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of presystemic elimination of gastro intestinal tract and depending on the particular drug. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). In general, the delivery of a drug requires some type of dosage form, present in the oral cavity, to release a drug, which then diffuses through the mucosa into the local blood circulation and is then taken further to the systemic blood circulation. Buccal drug delivery has several advantages over peroral delivery. Administration of compounds via the mucosa of the oral cavity avoids presystemic metabolism in the gastrointestinal tract (GIT) and hepatic first-pass elimination. In addition, the buccal mucosa is a well vascularized tissue and is easily accessible for both application and removal of a delivery device. It's having facility to include permeation enhancer in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.

Adhesion as a process, simply defined as the ''fixing" of two surfaces to one another. There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed ''bioadhesion", furthermore if this adhesion occurs on mucosal membranes it is termed ''mucoadhesion". Bioadhesion can be defined as the binding of a natural or synthetic polymer to a biological substrate. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and is permeable to many pharmacologically active agents. [1-5]

MATERIALS & METHODS

Pre-Formulation Study[6]
Infra- Red Spectroscopy

Infra red spectroscopy can be used to investigate and predict any possible physicochemical interactions between different components in a formulation and therefore, it can be applied to the selection of suitable, chemically compatible excipients. The aim of the present study was to find out the possible interaction between the selected polymer chitosan and the drug carvedilol and also to identify the compatibility between the drug and the polymer.

10 mg of the sample and 30 mg of potassium bromide were taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10 Kg/cm^2 using a hydraulic press. The pellet was kept on the same sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} and 2000 cm^{-1} to 400 cm^{-1} in Perkin Elmer FT-IR spectrophotometer. Samples were prepared for the pure drug, pure polymer, physical mixture of drug and polymer. The spectra obtained through those samples were compared and interpreted for shifting of functional peaks, and appearance or disappearance of new peaks.

Preparation of buccal patches

Buccal patches of carvedilol phosphate were prepared by using suitable amount of combinations of Chitosan, PVP K 30, PVP K 90, HPMC, and propylene glycol as plasticizer.

Optimization and study on effect of combination of polymers on film characteristics.

For studying the effect of different combinations of polymers on film characteristics and optimizing the formula for drug incorporations, we prepared three different combinations of polymers were used.

Table 1: Combination of polymers

Combinations	Formulations	Ingredients				
		Chitosan	PVP K 30	PVP K 90	HMC	Propylene Glycol
C1	**BPF_1**	1%	0.2%	-	-	5%
	BPF_2	1%	0.3%	-	-	5%
	BPF_3	1%	0.4%	-	-	5%
	BPF_4	1%	0.5%	-	-	5%
C2	**BPF_5**	0.8%	0.6%	0.2%	-	5%
	BPF_6	0.6%	0.6%	0.4%	-	5%
	BPF_7	0.4%	0.6%	0.6%	-	5%
	BPF_8	0.2%	0.6%	0.8%	-	5%
C3	**BPF_9**	0.8%	0.1%	0.5%	0.3%	5%
	BPF_{10}	0.8%	0.2%	0.4%	0.3%	5%
	BPF_{11}	0.8%	0.3%	0.3%	0.3%	5%
	BPF_{12}	0.8%	0.4%	0.2%	0.3%	5%

PHYSICAL PROPERTIES[7,8,9]

Physical Appearance and Surface Texture:
Physical appearance and surface texture evaluation includes visual inspection and evaluation of texture by feel or touch.

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

Thickness
The thickness of the patch was measured 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.

Percent Swelling Index
Diameter method
The polymeric patches are cut in to small patches of 1.5 cm diameter. This patch was placed on the surface of the agar plate and the diameter at different time intervals where taken up to 5 hrs and the percentage swelling index was calculated using the formula,

$$SD\% = Dt - Do / Do \times 100$$

SD% = % swelling by diameter method
Dt = diameter of swollen patch after time t
Do = original patch diameter.

Folding Endurance

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. 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.

Surface pH

Buccal patches were left to swell for 1 hour on the surface of the agar plate, the agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and the solution was poured into the petridish, it was allowed to stand until it 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.

MECHANICAL PROPERTIES [9]

Tensile Strength: The tensile strength of buccal patch refers to tension or force required to tear of the patch apart into two pieces. Tensile strength was determined using an instrument assembled in the laboratory.

Instrument
The instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance, one pan of the balance was replaced with one metallic plate having a hook for attaching the

film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan.

Method of Calculation: The definition of tensile strength as per American Standard for Testing Material (ASTM) standard tests principles is, "the maximum load during the tensile strength test divided by the original minimum cross-sectional area of the specimen". Thus, tensile strength,

$$T = \frac{M \times g}{B \times t} \quad \text{Dynes/cm}^2$$

T= force at break/ initial cross-sectional area of sample.
Where, m = mass in grams, g = acceleration due to gravity 980 cm/sec², b = breadth of the specimen in cm,
t = thickness of sample in cm.

Percent Elongation at Break
The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100.

$$\text{Percent elongation at break} = \frac{LB - L0}{L0} \times 100$$

LB = length of the specimen in cm when it breaks,
L0 = original length of the specimen in cm.

The instrument and procedure is similar to that used for tensile strength.

Bioadhesive strength [10]

Measurement of Bioadhesive Strength
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 physical balance. 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. At the same side, a platform was maintained in the bottom in order to fix the model mucosal membrane.

Method: The fabricated balance was used for the bioadhesion studies. The bovine cheek pouch excised and washed was fixed to the platform. The mucoadhesive patch was fixed of 3 cm², was fixed to the stainless steel lamina using an 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 20gms 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. Force required detaching 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.

PREPARATION OF DRUG LOADED PATCHES

By physicochemical evaluation from different polymer combinations three formulations were optimized for drug loading.

Table 2: Drug loaded batches

Amount of drug/ amount of polymer	30 mg/15ml	40 mg/15ml	50 mg/15ml	60 mg/15ml
BPF_4	BPF_4D_1	BPF_4D_2	BPF_4D_3	BPF_4D_4
BPF_5	BPF_5D_1	BPF_5D_2	BPF_5D_3	BPF_5D_4
BPF_{10}	$BPF_{10}D_1$	$BPF_{10}D_2$	$BPF_{10}D_3$	$BPF_{10}D_4$

Evaluation of carvedilol phosphate polymeric patches.

Drug Content Determination[11]
The weight of whole patch was determined and cut in to 2cm². For determining the drug content, a single piece of patch was taken and crushed in a mortar using pestle. 0.1 N HCl was added and triturated to completely dissolve the drug it was then filtered and diluted if necessary. The absorbance of the solution was measured using UV spectrophotometer at 241nm and the drug loading was calculated. Percentage drug loading was calculated using formula.

% drug loading = Practical loading X100 / Theoretical drug loading

In vitro release[12]
The *in vitro* release study was carried out using USP dissolution apparatus type 2 in 300ml phosphate buffer pH 6.6 at 50 rpm. A 2cm² patch was taken and attached to a glass slide in order to prevent floating of patch over the dissolution media. The in vitro release study was carried out for six hours. 5ml of samples were withdrawn at various times interval, replacing with fresh medium each interval, absorbance of the samples were measured at 241 nm, and the cumulative percentage release was calculated

Interpretation of data[13]
Determination of order of release of drug from buccal patch by Graphical method

To determine the order of release of drug from buccal patch by graphical method using the dissolution data, a graph was plotted with % drug release Vs time. Zero order release can be confirmed if a straight line or linearity is obtained. To find out the release rate constant, the slope of the curve was found out and multiplied with 2.303. Regression coefficient of the curve was determined to confirm the correlation between X and Y.

In the second stage, using the same dissolution data, a graph was plotted with log % remaining Vs time. If a straight line or linearity is observed, it can be confirmed that the drug release follows first order kinetics. The slope of the graph was found out and multiplied with 2.303 to obtain the first order rate constant k_1. Regression co-efficient of the graph was found out to confirm the correlation between X and Y.

Mechanism of drug release study

In order to predict and correlate the release behaviour of drug from the hydrophilic matrix, it is necessary to fit the *in vitro* release data in to a suitable model. Hence the dissolution data were fitted according to the well known exponential equation, which is often used to describe the drug release behaviour from a polymeric system. The equation which is used to describe drug release mechanism is:

$$M_t/m_\alpha = kt^n$$

Where, M_t/m_α is the fraction release of the drug,'t' is the release time, 'k' is the constant, which indicates the properties of the macromolecular polymeric system, and 'n' is the release exponent indicative of the mechanism of release. The 'n' value was used for the analysis of drug release mechanism from drug loaded buccal patches. The 'n' value was determined for all batches of drug loaded buccal patches by graphical method, which is explained below.

In the first stage, a graph plotted with log % time Vs log time. If a straight line is obtained, then the regression co-efficient was found out to confirm the linearity between X and Y. The slope (n) of the line was found out and if

n≤ 0.5 : The release is by Fickian diffusion
n> 0.5 and <1 : The release mechanism is swelling
n=1 : Release is by case II transport release mechanism

RESULTS

Infra- red spectroscopy

In order to investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies were carried out. IR spectrum for pure drug and physical mixture of drug-polymers were obtained and analyzed for principle peaks.

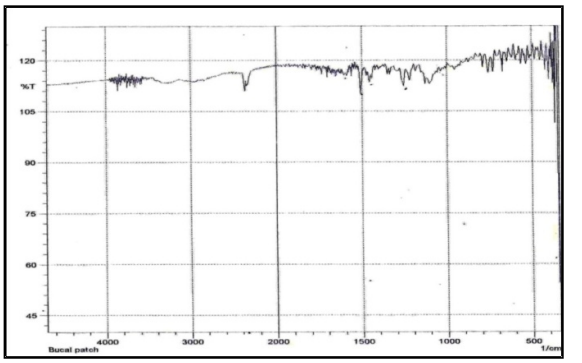

Figure 1: IR Spectrum of drug with polymers

Table 3: Physical evaluation results

	Appearance	Texture	Folding Endurance	Swelling-index	Average Weight(mg)	Thickness (mm)	Surface pH	Tensile strength (N/m^2)	Bio adhesive strength ($kg/m/s^2$)
BPF_1	Smooth	Less flexible	300	80	7.5	0.06	7	4.1 X 10^6	10.06
BPF_2	Smooth	Brittle	90	86	7.5	0.06	7	4.6 X 10^6	10.06
BPF_3	Smooth	Brittle	80	80	7.5	0.06	7	5.6 X 10^6	10.06
BPF_4	**Smooth**	**Flexible**	**335**	**120**	**7.5**	**0.06**	**7**	**6.8 X 10^6**	**10.06**
BPF_5	**Smooth**	**Flexible**	**341**	**86**	**9**	**0.03**	**7**	**9.6 X 10^6**	**8.73**
BPF_6	Smooth	Flexible	321	75	9	0.03	7	5.7 X 10^6	8.73
BPF_7	Smooth	Flexible	306	78	9	0.03	7	6.0 X 10^6	8.73
BPF_8	Smooth	Flexible	311	81	9	0.03	7	6.0 X 10^6	8.73
BPF_9	Smooth	Flexible	310	78	7	0.04	7	4.2 X 10^7	9.4
BPF_{10}	**Smooth**	**Flexible**	**345**	**84**	**7**	**0.04**	**7**	**4.3 X 10^7**	**9.4**
BPF_{11}	Smooth	Flexible	330	80	7	0.04	7	4.1 X 10^7	9.4
BPF_{12}	Smooth	Flexible	320	81	7	0.04	7	4.1 X 10^7	9.4

From the physical evaluation results three formulas BPF_4, BPF_5, BPF_{10} were selected for drug loading.

Table 4: Drug content evaluation

Formulas	BPF_4 D_1	BPF_4 D_2	BPF_4 D_3	BPF_4 D_4	BPF_5 D_1	BPF_4 D_2	BPF_5 D_3	BPF_5 D_4	BPF_{10} D_1	BPF_{10} D_2	BPF_{10} D_3	BPF_{10} D_4
Percentage drug loading	96.44	92.88	87.07	84.04	96.8	92.5	87.2	83.9	96.5	93.44	91.8	87.47

All the drug loaded batches showed a saturation capacity with that of the selected polymers at a concentration of 30mg/15ml of polymer.

In Vitro Dissolution Study

Batches shows best drug loading is selected for in vitro dissolution study.

Table 5: In vitro release study

Time in min	Cumulative % released BPF_4D_1	Cumulative % released BPF_5D_1	Cumulative % released $BPF_{10}D_1$
0	0	0	0
5	1.49	6.1	6.4
10	5.33	11.17	8.24
15	14.79	22.63	11.74
30	20.45	33.17	16.4
45	37.31	52.21	40.17
60	44.76	78	55.5
120	63.62	91.51	78.52
180	88.76		91.86
240	92.84		

Determination of order of release

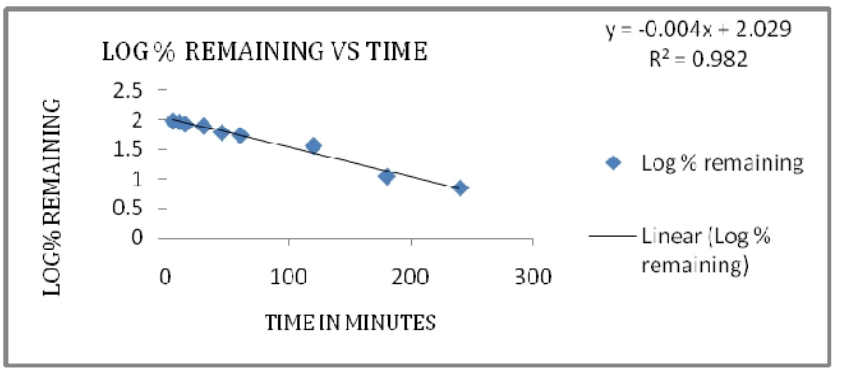

Figure 2: Order of release of formula BPF_4D_1

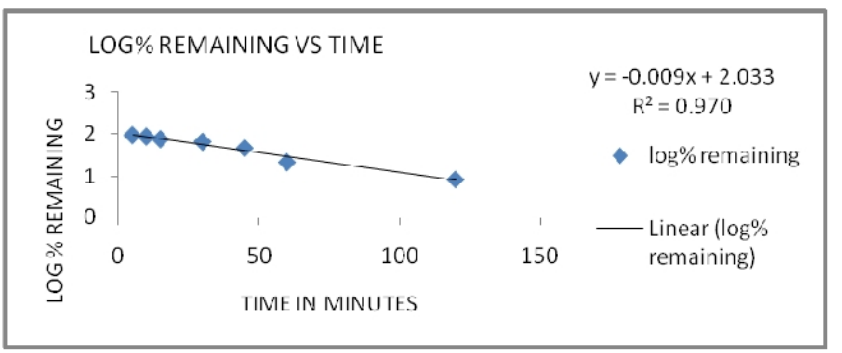

Figure 3: Order of release of formula BPF_5D_1

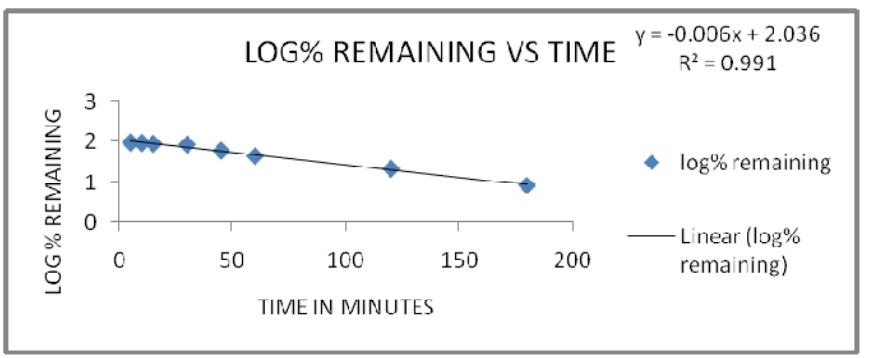

Figure 4: Order of release of formula $BPF_{10}D_1$

To determine the order of release for each batch, percentage drug remaining to be released Vs time graph was plotted, and log percentage drug remaining Vs time graph also plotted. Regression values of two graphs were determined, linearity was observed in log percentage drug remaining Vs time. So the kinetic release study showed that the all the drug loaded buccal patches of carvedilol phosphate (BPF_4D_1, BPF_5D_1, $BPF_{10}D_1$) followed first order release.

DISCUSSION

The selected drug carvedilol phosphate shows saturation capacity to all the combination of polymer at a concentration of 30mg/15ml. The in vitro release studies shows that there was an increase in the extend of duration of drug release with increase in concentration of chitosan in the formula. Kinetic of release of drug from all the drug loaded batches were found to follow first order.

The formulated buccal patches of carvedilol phosphate was found to be suitable buccal delivery system to avoid the first pass metabolism of carvedilol phosphate which will have other added benefits like longer duration of action and quicker onset of action as compared to tablets of carvedilol phosphate.

ACKNOWLEDGEMENT

I am deeply indebted to my research guide, Dr. K. Santhi under whose able and invaluable guidance, this entire research work was successfully completed. I am thankful to her constant source of encouragement and support, which provided to impetus and paved the way for the successful completion of the research work. It is my privilege to express my heartfelt thanks to Dr. Y. HariBabu, M.Pharm, PhD, Principal, Mr. Sajeeth C.I, Vice Principal, Grace College of Pharmacy, Palakkad, for providing me all facilities and encouragement throughout the research work. A special thanks to Mr.Praveen.R, Ranbaxy research laboratories Gurgaon,for providing the Drug Sample of carvedilol phosphate. I wish to express my gratitude to Dr.M.Ramanadhan, principal, PSG college of pharmacy, Coimbatore for providing the facilities for IR spectroscopy.

REFERENCES

1. R.S. Hirlekar,V.J. Kadam, Design of Buccal Drug Delivery System For A Poorly Soluble Drug Asian Journal of Pharmaceutical and Clinical Research Vol.2 Issue 3, July-September 2009.
2. Amit Gupta, Ram S. Gaud, S. Ganga, Development of Buccal adhesive formulations using in-situ formation of interpolymer complex and optimization using Box-Benhken design, International Journal of Advances in Pharmaceutical Sciences 2010 volume.1.
3. S. Roy, K. Pal, A. Anis, K. Pramanik and B.Prabhakar, Polymers in Mucoadhesive Drug Delivery System: A Brief Note, Designed Monomers and Polymers 2009 issue12,page no 483- 495.
4. Vamshi Vishnu Yamani, Ramesh Gannu, Chandrasekhar Kolli, M. E. Bhanoji Rao, MadhusudanRao, Yamsani, Development and *in vitro* Evaluation of Buccoadhesive Carvedilol tablets, Actapharmaceuticasciencia (2007) issue *57*, page no:185–197
5. Claudia Juliano, Massimo Cossu, Paola Pigozzi, Giovanna Rassu, and Paolo Giunchedi. Preparation, In Vitro Characterization and Preliminary In Vivo Evaluation of Buccal Polymeric Films Containing Chlorhexidine, American Association of Pharmaceutical Scientists2008.
6. Liji Jacob, C.I Sajeeth, K Santhi, design, development and evaluation of mucoadhesive patches of nifidipine for buccal delivery, Asian journal of pharmaceutical science and technology, Vol 2, issue1, 2012.
7. J. Thimmasetty, G.S Pandey and P.R Sathesh Babu, Design and *in vivo* evaluation of carvedilol buccal mucoadhesive patches, Pakistan. Journal of Pharmaceutical Science. Issue .21, July 2008, page no.241-248.
8. Mohammed Jafar, Sadath Ali, Studies on meloxicam solid dispersion incorporated buccal patches, Int. Res. J. Pharm. 2011;2(5): 220-227
9. Sarath chandran C, KV. Shijith, KV . Vipin and Ann Rose Augusthy, Formulation and evaluation of bisoprolol fumarate buccal patches by using selected polymers, International journal of pharmaceutical, chemical and biological sciences,
10. Preetha S Panicker, V Siva Kumar, A.Arunachalam, M Karthikeyan, S. Ashutosh Kumar, S Manidipa, Measurement of Bioadhesive Strength Mucoadhesive Buccal patches, Design of an *In- Vitro* Assembly International Journal of Contemporary Research and Review, November, 2010Volume 01, Issue 06.
11. J Varshosaz, S Karimzadeh, Development of Cross- linked Chitosan Film for Oral Mucosal Delivery of Lidocaine, Research in Pharmaceutical Sciences April 2007 volume 2 ,page 43-52.
12. Jobin Jose, Sreekanth M.C, Formulaton and evaluation of mucoadhesive chitosan buccal patch of labetalol hydrochloride, Pharma science monitor an international journal of pharmaceutical sciences Vol-3, Issue-3, July-2012
13. Subhash V. Deshmane, Madhuri A. Channawar, Anil V. Chandewar, Unmesh M. Joshi, Kailash R. Biyani, Chitosan based sustained release mucoadhesive buccal patches Containing Verapamil HCl, International Journal of Pharmacy and Pharmaceutical Sciences, volume 1, Nov-Dec 2009.

Cite this article as:

Sreekanth M.C, Anusha Ajayakumar, K. Santhi. Formulation and evaluation of buccal patches of Carvedilol phosphate. Int. Res. J. Pharm. 2016;7(8):22-27 http://dx.doi.org/10.7897/2230-8407.07892

Source of support: Nil, Conflict of interest: None Declared