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Evaluation of Tamarind Seed Polysaccharide (TSP) as a Mucoadhesive and sustained release component of nifedipine buccoadhesive tablet & Comparison with HPMC and Na CMC.

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ABSTRACT : The buccal mucoadhesive tablets of nifedipine were fabricated with objective of avoiding first pass metabolism and prolonging duration of action. The mucoadhesive polymers used in formulations were carbopol (cp934), hydroxyl propyl methyl cellulose (HPMC K4M), carboxy methyl cellulose (CMC), and tamarind seed polysaccharide (TSP) .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 tablets with fresh goat buccal mucosa as a model tissue. The best mucoadhesive performance and in vitro drug release profile were exhibited by the tablet containg carbopol and TSP in the ratio of 1:1. This formulation was more comfortable to the user due to less erosion, faster hydration rate, and optimum pH of surrounding medium.

Keywords: Buccal mucoadhesive tablet, Tamarind seed polysaccharide, Bioadhesive Strength, In vitro retention time, Nifedipine.

1. INTRODUCTION

Nifedipine, a systemic calcium channel blocker, is a practically water insoluble and light-sensitive drug used in angina pectoris and hypertension [1]. As its biological half-life is about 2 h and is eliminated rapidly, repeated daily administrations are needed to maintain effective plasma levels [2]. It shows a low and irregular bioavailability of about 50% after oral administration with a high first pass effect [3]. It has been suggested that drugs with biological half-lives in the range of 2–8 h are good candidates for sustained-release formulations [4]

A sustained-release formulation of nifedipine has become available [5]. Coated granules and matrix tablets [6], polyacrylate– polymethacrylate microspheres prepared by the solvent evaporation process [7], microcapsules and solid dispersions of nifedipine in polyvinylpyrrolidone (PVP)- microcrystalline cellulose [1] and sustained-release tablets containing hydroxypropylmethyl cellulose (HPMC) and cross-linked sodium carboxymethyl cellulose (CMC) [8] are controlled-release forms of this drug reported so far.

The short half-life and severe first pass metabolism of nifedipine makes it suitable for administration via a buccal delivery system that provides controlled drug delivery, bypassing first pass effect. Successful buccal delivery requires at least three of the following: (a) a bioadhesive to retain the drug in the oral cavity and maximize the intimacy of contact with the mucosa; (b) a vehicle that releases the drugs at an appropriate rate under the conditions prevailing in the mouth; and (c) strategies for overcoming the low permeability of the oral mucosa [9]. Mucoadhesive drug delivery systems promote the residence time and act as sustained-release dosage forms [10]. Three steps of formation of bioadhesive bonds are: (a) wetting and swelling of polymer; (b) entanglement of polymer and mucin chains; and (c) formation of weak chemical bonds between entangled chains [9]. A mucoadhesive nasal formulation of nifedipine containing carbopol 941 gels with polyethylene glycol (PEG) 400 has been reported by Morimoto et al. [11]. Save and Venkitachalam [12] prepared a buccoadhesive erodible carrier consisting of sodium alginate, mannitol, and PEG 6000 for nifedipine.

The aim of this work was to develop and characterize a buccoadhesive sustained release tablet of nifedipine. The buccal route was chosen because of its good accessibility, robustness of the epithelium, facile removal of the dosage form, relatively low enzymatic activity, and natural clearance mechanisms for elimination of the drug from buccal area, satisfactory patient acceptance and avoiding the hepatic first pass metabolism [13]. Apart from the overall increased bioavailability, because of bypassing the first pass effect and sufficient time to produce therapeutic effect [14], an important advantage of buccal delivery for nifedipine is also potentially better control of plasma levels, typically lower variation in bioavailability, reduced costs of the drug because of application of much lower doses than necessary for oral products.

2. MATERIALS AND METHODS

2.1 MATERIALS

Nifedipine was obtained as a gift sample from Suchem Lab, Ahemdabad. Carbopol (cp 934), Hydroxylpropyl methyl cellulose (HPMC K4M), Sodium carboxy methyl cellulose (Na CMC) was obtained from loba chemie, Mumbai. Tamarind seed polysaccharide powder (TSP) was isolated from tamrindus indica seed. All other materials used are of analytical grade.

2.2 METHODOLOGY

2.2.1 ISOLATION OF TSP

The alcohol-insoluble fraction from the water extract of tamarind seed meal, constituting 60 to 65 per cent of the husked kernel, has been described as a rich source of polysaccharides. TSP was prepared following methods by Rao et al., [15, 16, and 17] in three batches on a laboratory scale. To 20g of tamarind kernel powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute alcohol by continuous stirring. The product was pressed between felt. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60° C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range. The particle size range of 150-75 microns was used for preparation of tablets.

2.2.2 PREPRATION OF BUCCAL MUCOADHESIVE TABLETS

The tablets were prepared by direct compression methods, using different combination of polymers shown in Table 1. The buccal tablets were prepared using carbopol 934 as a primary a mucoadhesive polymer and HPMC K4M, Na CMC and TSP as secondary mucoadhesive polymers. The effect of secondary polymers on drug release and mucoadhesion was studied.

2.2.3. EVALUATION OF BUCCAL MUCOADHESIVE TABLET

2.2.3.1 DETERMINATION OF PHYSICOCHEMICAL PARAMETERS

Twenty tablets were weighed individually and the average weight was determined. Percentage deviation was calculated and checked for weight variation. Thickness was measured using vernier calipers. Five tablets of each formulation were taken and amount of drug present in each tablet was determined. The surface pH of the tablets was determined in phosphate buffer pH 6.2 in order to investigate the possibility of any irritation in the oral cavity. The tablets were kept in contact with phosphate buffer pH 6.2 for 2 h and pH was noted by using universal pH paper.

2.2.3.2 BIOADHESIVE STRENGTH

Bioadhesive strength of tablets was measured on modified physical balance using method described by gupta et al [18] Shown in figure 1. The goat buccal mucosa was used as a model mucosal membrane and a Krebs solution as a moistening fluid. The experiment was repeated for three times for each formulation. Two-arm balance method reported by Parodi [19] with minor modifications and he had also used to check and to validate the results of the modified tensiometry method and the correlation between the results obtained from these two techniques was established by Parodi.

2.2.3.3 IN VITRO RETENTION TIME OF BUCCAL MUCOADHESIVE TABLETS

The in vitro retention time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised goat mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 750 ml of phosphate buffer, pH 6.2, at 37^0c. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (figure 2).The time for complete erosion or detachment from the mucosa was recorded.

2.2.3.4 SWELLING STUDIES

The swelling properties and the erosion characteristics of tablets were evaluated by determination of % of Hydration. Each tablet was weighed (W1) and immersed in a phosphate buffer at pH 6.2 for predetermined times (1, 2, 4 hr). After immersion, tablets were wiped off by the excess of surface water by the use of filter paper and weighed (W2). This experiment was performed in triplicate. The % hydration was calculated by formula using % hydration =W2 - W1/W1×100 and swelling of different formulations shown after 4 hours in figure 3.

2.2.3.5 IN VITRO RELEASE STUDY

The release study from mucoadhesive tablets were done using USP dissolution apparatus II (Rotating Paddle). In this study the 900 ml of phosphate buffer of pH 6.2 was used. The temperature of the bath maintained at 37^0c and

The paddle was rotated at 100 rpm, the samples of the dissolution medium were taken at an interval of one hour for 8 hours. The amount of drug released was determined spectrophotometrically at 237.5 nm. The % drug release was calculated using PCP disso software.

3. RESULTS AND DISCUSSION

The average weight of the tablet was found to be between 178.0 mg to 181.3 mg and maximum % deviation was found to be 0.75 from all formulations. The thickness of all tablets was found to be between 2.43 mm to 1.75 mm and % deviation in thickness was found to be 0.02 to 0.18.Percent drug content was found to be 97-99%.

The surface pH of all formulations was found in between 6 to 7 except F4, F5, F6 which were showing the pH less than 5, and F10 showing the pH less than 3. The surface pH of all formulations was found in range except F4, F5, F6 Showing the pH less than 5 because of carboxylic acids group present in Na CMC Polymers, while F10 showing the pH less than 3 because of the carbopol and hence even if it has bioadhesive property it can not be used alone in buccal mucoadhesive formulations. These results reveal that formulations provide an acceptable pH in the range of salivary pH (5.5-7.0) can not produce irritation to the buccal Mucosa.

The Table 2 shows the bioadhesive performance and in vitro retention time. The in vitro retention time is one of the important physical parameter of buccal mucoadhesive tablet which was recorded as per the procedure mentioned above. The results shows that F4, F5, F6 tablets shows lower in vitro retention time of 3 hours, While the HPMC and TSP groups tablets show the longer retention time of greater than 8 hours. The bioadhesive strength of tablet was dependent on the property of the bioadhesive polymers, which on hydration adhere to the mucosal surface and also on the concentration of polymer used. For In-vitro Retention time, the results shows that F4, F5, F6 tablets shows lower in vitro retention time due to erosion and faster fragmentation within 3 hours.

Swelling index was calculated with respect to time. The swelling index increased as the weight gain by the tablets increased proportionally with rate of hydration as shown in to the table 3 and Photograph of different formulations are shown in figure 3. Swelling index increases with respect to time because of hydration. Swelling index measurement could be done up to 2 hours with formulations containing Na CMC, because it loses its shape and size at the end of 2 hours. The F4, F5, F6 were shown the % swelling index in the range of 47-54% in 4 hours. This is because Na CMC dissolves in water giving the stable colloidal dispersion and thereby gets eroded to greater extent. The matrix erosion started to increase after around 1.5 hours because of hydration and dissolution of the Na-CMC.

The figures 4, 5 and 6 show the % drug release from formulations containing different polymers. Tablets from HPMC group shows the slower % drug release, these results were due to slower hydration and low viscosity of HPMC. Tablets from Na CMC group show the % drug release highest, this is due to the higher hydration and dissolution of Na CMC which forms colloidal dispersion. Tablets from the TSP group show the % drug release less than 91%, and hence it is comparable to Na CMC in drug release and also it was not erode as faster as Na CMC, so it is better for patient compliance.

4. CONCLUSION

The aim of present study was to evaluate TSP as a mucoadhesive, sustained release polymer and to develop bioadhesive drug delivery for nifedipine with prolonged effect and to avoid first pass metabolism. The mucoadhesive formulation of nifedipine, in form of buccoadhesive tablet were developed to a satisfactory level in term of drug release, bioadhesive performance, physiochemical properties, and surface pH with formulation containing carbopol and TSP in ratio of 1:1. The TSP is comparable with Na CMC in respect of drug release and bioadhesive strength but TSP is better than Na CMC because the erosion of tablets containing Na CMC is more and hence it won't be good feeling for patient in mouth.

Table 1. Composition of Buccal Mucoadhesive tablets.

Formulation	Nifedipine (mg)	Cp-934 (mg)	HPMC (mg)	Na CMC (mg)	TSP (mg)	Mg STEARATE (mg)
F1	30	74	74	-	-	2
F2	30	54	94	-	-	2
F3	30	37	111	-	-	2
F4	30	74	-	74	-	2
F5	30	54	-	94	-	2
F6	30	37	-	111	-	2
F7	30	74	-	-	74	2
F8	30	54	-	-	94	2
F9	30	37	-	-	111	2
F10	30	148	-	-	-	2

Table 2. Bioadhesive strength and in vitro retention time of different mucoadhesive tablets.

Formulations	Bioadhesive strength (gm)	In vitro retention time
F1	17.48	2 hours 46 minutes
F2	17.95	3 hours 15 minutes
F3	18.16	3 hours 20 minutes
F4	18.45	3 hours 45 minutes
F5	18.86	4 hours 50 minutes
F6	21.53	5 hours 9 minutes
F7	19.86	More than 8 hours
F8	19.05	More than 8 hours
F9	19.25	More than 8 hours
F10	19.65	5 hours 33 minutes

Table 3. Percent swelling of different formulations at different time.

Formulation code	% Swelling		
	1 hr	2 hr	4 hr
F1	73.73	134.06	216.48
F2	80.55	138.54	198.93
F3	100.10	144.91	170.10
F4	125.70	99.76	53.66
F5	148.42	102.16	48.04
F6	151.44	112.20	46.95
F7	125.73	224.58	277.47
F8	138.76	209.44	265.96
F9	131.57	199.46	236.78
F10	163.82	236.22	295.50

Figure 1. Modified physical balance for measurement of mucoadhesive strength

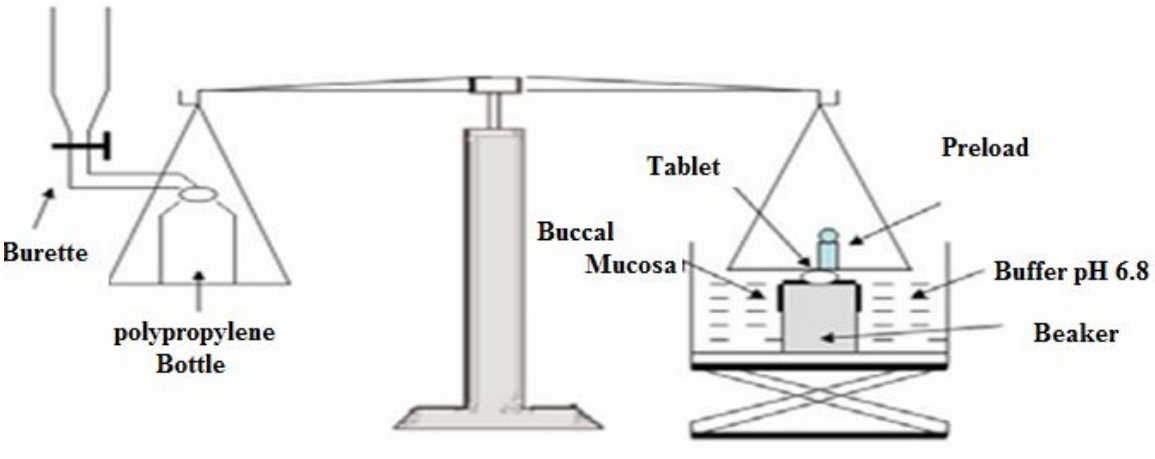


Figure 2.Schematic representation of in-vitro RetentionTime.

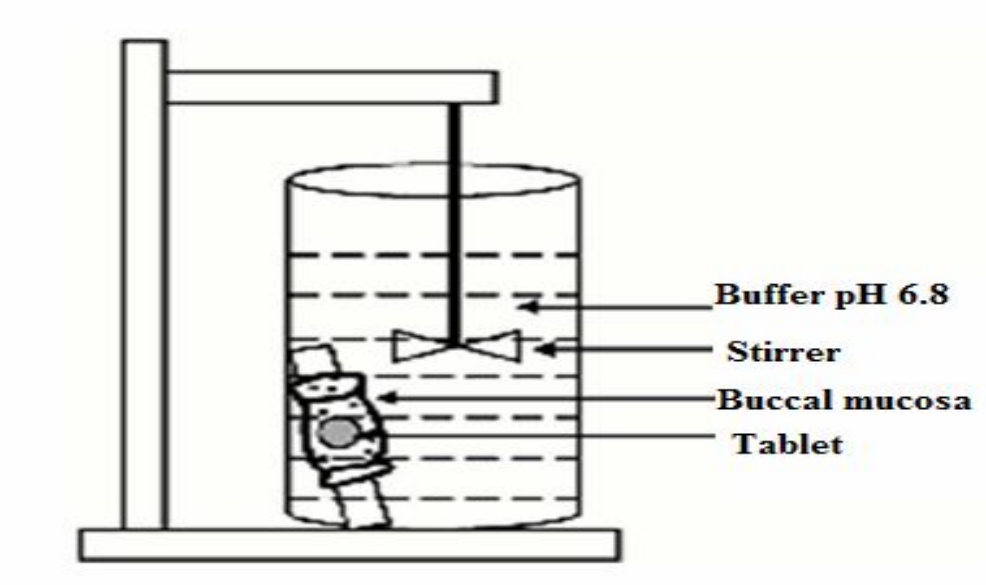
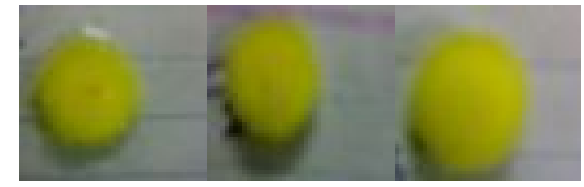


Figure 3. swelling of different formulations after 4 hours



F1 **F2** **F3**

F4 **F5** **F6**

F7 **F8** **F9**

F10

Figure 4. Dissolution profile of HPMC Group tablets containing Nefidipine

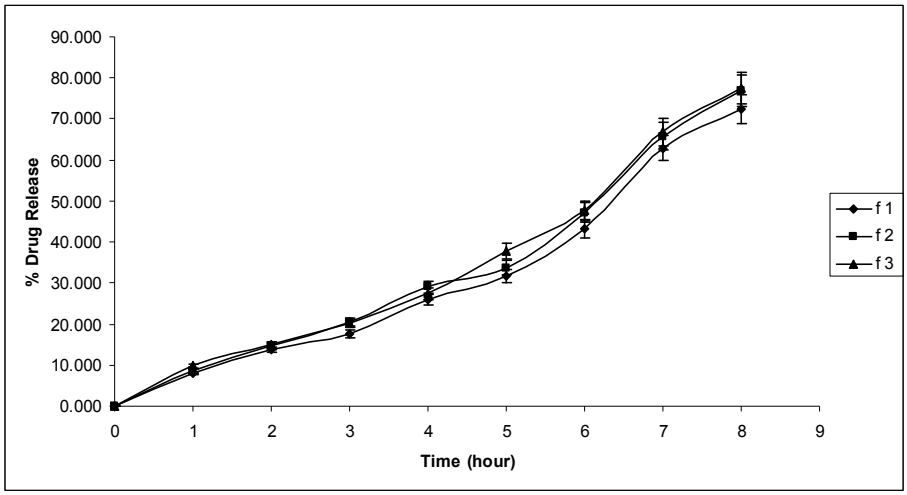


Figure 5 Dissolution profile of Na- CMC Group tablets containing Nefidipine

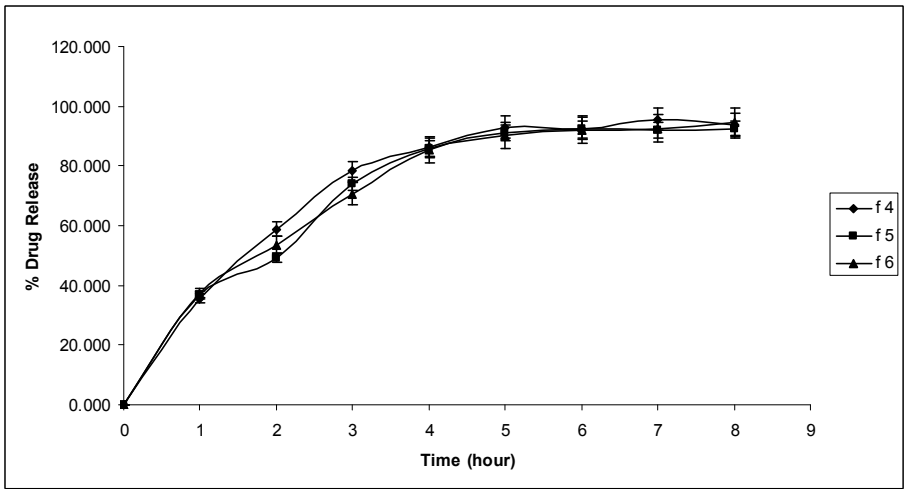
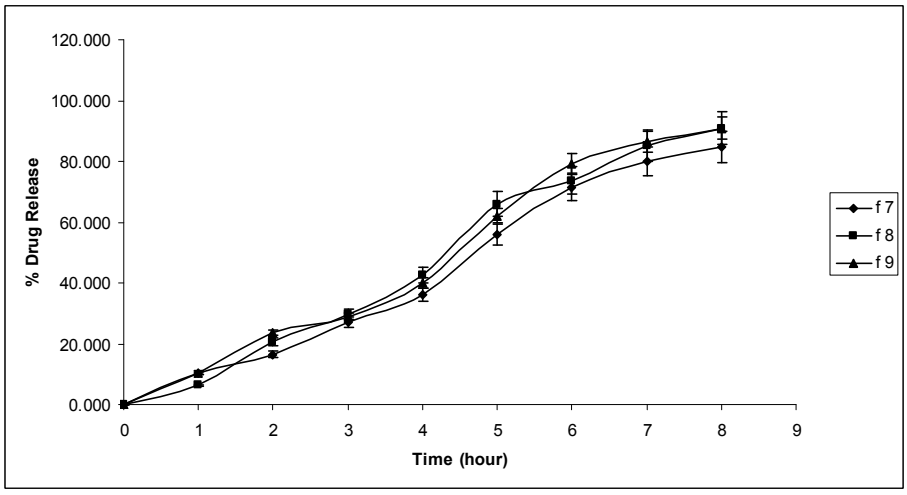


Figure 6 Dissolution profile of TSP Group tablets containing Nefidipine



5. ACKNOWLEDGEMENT

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6. REFERENCES

1. Chowdary KR, Ramesh KS, Controlled nifedipine release from microcapsules of its dispersions in PVP–MCC and HPC–MCC. Drug Dev. Ind. Pharm, 1995, 21: 1183-1192.

2. Murdock D, Brogden RN, Sustained release nifedipine formulations.

Drugs, 1991, 41:737–779.

3. Benet LZ, Øie S, Schwartz JB, Design and optimization of dosage regimens; pharmacokinetic data, in: J.G. Hardman, A. Goodman Gilman, L.E. Limbird (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed, McGraw-Hill, New York, 1996, 1675.

4. Longer MA, Ch'ng HS, Robinson JR, Bioadhesive polymers as platforms for oral controlled drug delivery. J. Pharm. Sci, 74:406–411.

5. PDR (Physicians' Desk Reference), 54th ed., Medical Economics Company Inc, Montvale, NJ, 2000 pp. 331, 673, 2363.

6. Kohri N, Mori KI, Miyazaki K, Arita T, Sustained release of nifedipine from granules. J. Pharm. Sci, 1986, 75:57–61.

7. Barkai A, Pathak YV, Benita S, Polyacrylate (Eudragit retard) microspheres for oral controlled release of nifedipine. Drug Dev. Ind. Pharm, 1990, 16:2057–2075.

8. Maggi L, Torre ML, Giunchedi P, Conte U, Supramicellar solutions of sodium dodecyl sulphate as dissolution media to study in vitro release characteristics of sustained release formulations containing an insoluble drug: nifedipine. Int. J. Pharm, 1996, 135:73–79.

9. Chickering DE, Mathiowitz E, Definitions, mechanisms, and theories of bioadhesion, in: E. Mathiowitz, D.E. Chickering, C.M. Lehr, C.M. Lehr (Eds.), Bioadhesive Drug Delivery Systems, Fundamentals, Novel Approaches, and Development, Marcel Dekker Inc., New York, 1999, 1.

10. Ahuja A, Khar RK, Ali J, Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm, 1997, 23:489–515.

11. Morimoto K, Tabata H, Morisaka K, Nasal absorption of nifedipine from gel preparation in rats. Chem. Pharm. Bull, 1987, 35:3041– 3044.

12. Save T, Venkitachalam P, Buccoadhesive tablets of nifedipine: standardization of a novel buccoadhesive erodible carrier. Drug Dev. Ind. Pharm, 1994, 20:3005–3014.

13. Burgalassi S, Panichi L, Saettone MF, Jacobsen J, Rassing MR, Development and in vitro/in vivo testing of mucoadhesive buccal patches releasing benzylamine and lidocaine. Int. J. Pharm, 1996, 133:1–7.

14. Prudat-Christiaens C, Arnaud P, Allain P, Chaumeil JC, Aminophylline bioadhesive tablets attempted by wet granulation. Int. J. Pharm, 1996, 141:109–116.

15. Nandi RC, A Process for preparation of polyose from the seeds of Tamarindus indica, Ind. Pat, 142092, 1975.

16. Rao PS, Srivastav HC, Tamarind. In Indusrtial Gums, (Ed.) R.L. Whistler, Academic Press, 2nd Ed, New York, 1973, 369-411.

17. Rao PS, Extraction and purification of tamarind seed polysaccharide. J Sci Ind Research, 1946, 4:705.

18. Gupta A, Garg S, Khar RK, Interpolymer complexation and its effect on bioadhesive strength and dissolution characteristics of buccal drug delivery systems. Drug Dev Ind Pharm, 1994, 20:315- 325.

19. Parodi B, Russo E, Caviglioli G, Cafaggi S, Bigbardi G, Development and characterization of a buccoadhesive dosage form of oxycodane hydrochloride. Drug Dev Ind Pharm, 1996, 22:445-450.

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