EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 6
461-468
Year: 2019

FORMULATIONS AND *IN VITRO* EVALUATION STUDIES OF BUCCAL ADHESIVE RANOLAZINE TABLETS USING NATURAL EDIBLE MUCOADHESIVES

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Article Received on 30/03/2019 **Article Revised on 11/04/2019** **Article Accepted on 12/05/2019**

ABSTRACT
Mucilage's of plant origin have been used widely as demulcent because of their unique properties to bind with the mucus membrane. Isolation of water-soluble components from the natural edible sources was carried out by cold/hot aqueous extraction process followed by the organic solvent precipitation. The yield of PD, PJ, AA and AE was ≈5.5, 4.99, 3.49, 3.88 % w/w respectively to the initial weight. The isolated mucoadhesive materials obtained from natural sources were proved to be safe and free from toxic or adverse effects. Swollen volumes after 24 hours of hydration was found to be 12.1, 12.4, 13.3, and 18.3 indicating their moderate swellability compared to 27.4 of CP 934 P, 25.7 of sodium alginate, 1.2 of guar gum and 6.4 of HPMC. The moisture sorption capacities of PD & PJ are very less. The loss on drying of PD, PJ and AA & AE were less than the official limit of 6%. The isolated mucoadhesive material possessed comparable shear and tensile strengths to the commercially available GRAS category polymers and higher than the other natural polymers such as sodium alginate and guar gum. Adhesive cups were studied for their mucoadhesive strengths by using the specially fabricated apparatus. Tensile, shear and peel strengths were calculated after five minutes of contact time. The AC 18, AC 17, AC 19 and AC 22 formulations exhibited residence times of 4.98, 4.82 and 5.08 hours respectively. AC 17, AC 18, AC 19 and AC 22 formulations from the investigated materials were selected for further studies. The thickness of NBATs using the isolated material falls between 1.14 to 1.28 mm and weight between 32.8 to 39.8 mm, suggesting its suitability for ease of administration without any discomfort. Results such as percent friability (0.21 to 0.87%) and hardness (3.11 to 4.42 g/cm2) were found to be within the recommended values. The observed parameters such as duration of stay of the dosage form, its intactness at the affixed site, duration of maintenance of its structural integrity, palatability, effect on salivary secretion, discomfort to talk due to swelling or stickiness, possible irritation during and after removal of dosage form and feeling of dryness, bitterness etc. The photomicrographs suggest that considerable damage was not found after the administration of NBATs. The FTIR Spectra's of Ranolazine, NBATs 3, 7, 11, and 15 suggest that Ranolazine has not undergone any unacceptable interactions with the mucoadhesive polymers isolated from the natural edible sources. The DSC thermographs suggest that there are no significant interactions between the Ranolazine with the additives used in the formulation, thus the additives used and the methods adopted are acceptable. Results in vitro dissolution studies suggest that the NBATs could release the drug following first order in formulations without the inclusion of mucoadhesive material in the core tablets, but followed Higuchi diffusion or Korsmeyer – Peppas patterns after the inclusion of the same. In vitro dissolution studies was found that less than 4% of drug diffused through the backing layer in four hours of study compared to 5.87% in sodium alginate and 6.18% in guar gum. The results suggest that the mucoadhesive material under investigation has not allowed the drug to diffuse through its backing layer enabling unidirectional release pattern.

KEYWORDS: Mucilages of plant, Ranolazine, Mucoadhesive polymers, sodium alginate and guar gum, First order, Higuchi diffusion or Korsmeyer – Peppas, Male New Zealand albino rabbits.

INTRODUCTION
Pharmaceutical dosage form development is the combination of an art as well as a science with the sole objective to produce a dosage form that is efficacious, patient friendly, stable, economical and delivers the drug as close as possible to the intended target with minimal adverse effects. Conventional forms of drug administration, in many cases, have been supplanted by the advent of novel drug delivery systems. The pharmaceutical companies are presently seeking innovative dosage forms by way of novel drug delivery systems as they represent strategic tool for expanding

markets and indications, extending product life cycles and generating newer opportunities.[1] NDDS is no longer a theory. It is a reality and this is illustrated by the fact that around 13% of the current global pharmaceutical market is accounted for NDDS. Among the NDDS, transmucosal drug delivery market recorded second highest growth in the last five years with 171% where as overall market growth stands at 106%.[2]

Rapid developments in the field of molecular biology and gene technology resulted in generation of many new drugs in large number including peptides, proteins, polysaccharides, nucleic acids and other molecules possessing superior pharmacological efficacy and site specificity. But, the main impediment for oral delivery of these drugs is their inadequate oral absorption due to extensive presystemic metabolism and instability in acidic environment.[3] As a result, the full therapeutic potential of many drugs cannot be realized; hence administration through highly expensive and less patient friendly parenteral route is inevitable. Further, parenteral route is most hazardous due to incidences of anaphylaxis, extravasations and infection risk. Serious drawbacks associated with parenteral route and poor drug bioavailabilities have led to investigate new alternative non-invasive drug delivery systems.[4] Transepithelial drug delivery across skin or absorptive mucosae seems to offer many benefits such as improved bioavailability and, hence possible to lower drug doses, thereby less dose-related side effects than the oral route. In comparison, transmucosal delivery systems exhibit a faster delivery than do transdermal delivery systems. Also, delivery occurs in a tissue that is more permeable than skin and is less variable between patients, resulting in minimal inter subject variability. In addition, these systems could potentially be used to deliver drugs that exhibit poor and variable bioavailability due to significant hepatic first-pass metabolism.[5] The absorptive mucosae include buccal, sublingual, palatal, gingival, nasal, pulmonary, rectal, vaginal and ocular routes. On the other hand, in case of nasal delivery, availability of very small surface area for absorption as well as the large variability in mucus secretion could significantly affect drug absorption. Further, severe sensitivity to drugs causes significant irreversible damage to the mucosa. In pulmonary delivery, despite the enormous surface area available for absorption, the major challenge is the reproducible placement of drug in the alveolar region due to the mucociliary clearance, hence not suitable for sustained delivery. Vaginal, rectal and ocular mucosae offer many advantages, but poor patient compliance making them a feasible site for local applications rather than for systemic use. Sublingual mucosa is more permeable but not suitable for retentive delivery. Palatal and gingival routes are suitable for retentive drug delivery but has poor permeability coefficient.[6]

Among all transmucosal sites, buccal cavity was found to be the convenient and easily accessible site for the local or systemic delivery of drugs. Because of its expanse of relatively immobile smooth muscle, abundant vascularization, direct access to the systemic circulation through the internal jugular vein that bypasses hepatic first pass metabolism, makes it highly promising for delivery of drugs exhibiting poor oral bioavailabilities. Facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious advantages of buccal adhesive systems.[7] In order to improve bioavailability of administered drug across the buccal mucosa, several bioadhesive tablet systems have been the subject of a growing interest. Recent reports suggest that the market share of buccal adhesive drug delivery systems are increasing in the American and European market with the steady growth rate of above 10%.

MATERIAL

Ranolazine Procured from Sun Pharmaceutical Industries Ltd, India as a gift sample, Diazepam from M/S East India Pharmaceutical Works Ltd, Kolkata, India, Gummy exudates of Acacia Arabica Willd from Purchased from Local Market, Sodium alginate from Loba chemie, India, Guar gum from E-Merck (India) Hydroxypropyl methyl cellulose (HPMC5cps) and Carbopol 934p from s.d. fine-chem limited, India, Acetone, Isopropanol, Methonal, Chloroform and Buffered formalin from Merck India.

METHODS

Formulation of Novel Buccal Adhesive Tablets[8]

NBAT were prepared in a three-step process involving preparation of adhesive cups, core tablets and NBATs. The design of punches and dies and its respective dimensions was reported.

Preparation of Adhesive cups and granules[9-11]

The extracted natural materials were mixed with each other at varying proportions to find out the best possible combination that shows ideal qualities of bioadhesive material in respect of mucoadhesive strength, swellability, leaching of drug, *in vitro* residence time, and good flowing and handling properties. The granules for compression of adhesive cups were prepared by wet granulation method in the compositions. In formulation of adhesive cups, the respective mucoadhesive substance was mixed with the microcrystalline cellulose, 10% w/v PVP solution was used as granulating agent and then passed through sieve # 18. Granules were dried in a tray drier at $50 + 1^0$C for 6 hours, passed through sieve # 22. The granules were mixed uniformly with calculated quantities of powdered sucrose, vanillin and talc.

Preparation of core tablets[12-14]

Core tablets were formulated by direct compression method by mixing Ranolazine, microcrystalline cellulose, respective mucoadhesive substance, and purified talc. 10 mg of the mixture was weighed and directly compressed using 2.8 mm flat faced punches at the compression force to get tablets with the thickness of 0.8 mm. For human acceptability studies, placebo core tablets were prepared

by replacing Ranolazine with the lactose. Finally, NBATs were prepared by inserting core tablets into the respective cups manually and compressed with little force using 4.5 mm flat faced punches. The compositions used were given in the following Table. 1.

Table. 1. Compositions OF Formulations.

F. C	Ranolazine (mg)	PD (mg)	AA (mg)	AE (mg)	PJ (mg)	HPMC (mg)	CP (mg)	SA (mg)	GG (mg)	MCC (mg)	Talc (mg)
PD 1	3.5	0	--	--	--	--	--	--	--	6.3	0.2
PD 2	3.5	0.5	--	--	--	--	--	--	--	5.8	0.2
PD 3	3.5	1.0	--	--	--	--	--	--	--	5.3	0.2
PD 4	3.5	1.5	--	--	--	--	--	--	--	4.8	0.2
AA 1	3.5	--	0	--	--	--	--	--	--	6.3	0.2
AA 2	3.5	--	0.5	--	--	--	--	--	--	5.9	0.2
AA 3	3.5	--	1.0	--	--	--	--	--	--	5.3	0.2
AA 4	3.5	--	1.5	--	--	--	--	--	--	4.8	0.2
AE 1	3.5	--	--	0	--	--	--	--	--	64	0.2
AE 2	3.5	--	--	0.5	--	--	--	--	--	5.8	0.2
AE 3	3.5	--	--	1.0	--	--	--	--	--	5.2	0.2
AE 4	3.5	--	--	1.5	--	--	--	--	--	4.8	0.2
PJ 1	3.5	--	--	--	0	--	--	--	--	6.3	0.2
PJ 2	3.5	--	--	--	0.5	--	--	--	--	5.8	0.2
PJ 3	3.5	--	--	--	1.0	--	--	--	--	5.3	0.2
PJ 4	3.5	--	--	--	1.5	--	--	--	--	4.8	0.2
HPMC 1	3.5	--	--	--	--	0	--	--	--	6.3	0.2
HPMC 2	3.5	--	--	--	--	0.5	--	--	--	5.8	0.2
HPMC 3	3.5	--	--	--	--	1.0	--	--	--	5.3	0.2
HPMC 4	3.5	--	--	--	--	1.5	--	--	--	4.8	0.2
CP 1	3.5	--	--	--	--	--	0	--	--	6.3	0.2
CP 2	3.5	--	--	--	--	--	0.5	--	--	5.8	0.2
CP 3	3.5	--	--	--	--	--	1.0	--	--	5.3	0.2
CP 4	3.5	--	--	--	--	--	1.5	--	--	4.8	0.2
SA. 1	3.5	--	--	--	--	--	--	0	--	6.3	0.2
SA. 2	3.5	--	--	--	--	--	--	0.5	--	5.8	0.2
SA. 3	3.5	--	--	--	--	--	--	1.0	--	5.3	0.2
SA 4	3.5	--	--	--	--	--	--	1.5	--	4.8	0.2
GG 1	3.5	--	--	--	--	--	--	--	0	6.3	0.2
GG 2	3.5	--	--	--	--	--	--	--	0.5	5.8	0.2
GG 3	3.5	--	--	--	--	--	--	--	1.0	5.3	0.2
GG 4	3.5	--	--	--	--	--	--	--	1.5	4.8	0.2

Finally, NBATs were prepared by inserting core tablets into the respective cups manually and compressed with little force using 4.5 mm flat faced punches.

Characterization-Drug Excipient Compatibility Studies

FTIR studies

The I.R. spectrum of mucoadhesive substances, Ranolazine and optimized NBATs were recorded individually. The disc was made using 1 mg of sample in 100 mg potassium bromide and the spectra were recorded between 4000 cm^{-1} – 400 cm^{-1} using Shimadzu FTIR Spectrophotometer.[15-17]

Differential Scanning Colorimetry

DSC Thermographs of Ranolazine and optimized formulation of NBATs were recorded between 30.0^{O}C to 300.0^{O}C at the rate of 20.0^{O}C per minute under the environment of nitrogen.[18-19]

***In Vitro* dissolution studies**

In vitro dissolution studies of NBATs were conducted in P-3813 Phosphate buffered saline (pH 7.4, 250 ml) at 37°C by paddle method at 100 rpm by using USP XXII Electro Lab TDT- 08L eight-spindle dissolution apparatus[20]

To study the dissolution rate

NBATs were fixed at the bottom surface of dissolution chamber exposing the core tablets to the dissolution medium. Samples were withdrawn at regular time intervals for four hours and Ranolazine content was estimated by measuring at 236nm using JASCO V-550 UV/VIS Spectrophotometer. The dissolution profiles of the mean of the six replicates at each data points were determined. Release kinetics of Ranolazine from NBATs was evaluated through zero order, first order, Higuchi

diffusion, Korsmeyer - Peppas and Hixon Crowell plots and the results were reported and the corresponding plots were represented in Figures. The procedure was repeated six times for each batch of NBATs.[21-23]

RESULTS AND DISCUSSION

Mucilages or mucopolysaccharides of plant origin have been used widely as demulcent because of their unique properties to bind with the mucus membrane. The selection of the materials for the current investigation was based on their edibility, blandness, availability, and the economics. The selection of the process was based on previous literature giving utmost importance to preserve the components against thermal, enzymatic and hydrolytic degradation. The processes used were found to be effective in selective isolation of the material and the yielded material possesses good handling properties. The details of the extraction process, respective yield, and their physical properties such as pH, swollen volume, swelling capacity, moisture sorption capacity, loss on drying etc. The acute and subacute toxicity studies of extracted sample profile showed that the mucopolysaccharides did not cause any toxic effects on animals. After the observation for 14 days, in the case of sighting study, the data confirmed no hypersensitization of skin and irritation to eye. No ulceration or inflammation was observed on mucosal membrane and respiratory system respectively. On circulatory system, no sign of cardiac toxicities like increased heart rate, force of contraction or elevated blood pressure was observed. Abnormal toxic effects like neurotoxicity, anxiety or depression was also not observed. The motor coordination and body weight was observed to be normal. Hematological and biochemical parameters showed no changes on the normal blood counts. The heparinised and non-heparinised blood samples also showed normal profile and no gross lesions. The yield of PD, PJ, AA and AE was ≈5.49, 4.91, 3.46, 3.87 % w/w respectively to the initial weight. pH of 1% w/v solutions of PD and PJ was found to be 5.67, 6.68 respectively which is very closer to the pH of saliva ≈6.6 suggesting its non-irritability to the buccal mucosa. Swelling is the primary characteristic of any material to be a mucoadhesive substance, but over hydration causes slippery surface. Excessive swelling also causes loss of mechanical strength that is required to maintain the structural integrity of the solid dosage forms. Swollen volumes after 24 hours of hydration was found to be 12.1, 12.4, 13.3, 18.3 indicating their moderate swellability compared to 27.4 of CP 934 P, 25.7 of sodium alginate, 31.2 of guar gum and 6.4 of HPMC. Swelling was also assessed by the determination of swelling capacity and moisture sorption profile. Study of moisture sorption is also of considerable importance since it reflects the relative physical stability of dosage forms when stored under humid conditions. In all, this property showed that the AA & AE powders are sensitive to atmospheric moisture and should therefore be stored in airtight containers. But it was found that the moisture sorption capacities of PD & PJ are very less. The loss on drying of PD, PJ, AA & AE were less than the official limit of 6% stated in British Pharmacopoeia 2004. The weight required to detach the blocks/tissues attached together by the mucoadhesive solutions after specified contact times. The results suggest that the isolated mucoadhesive material possessed comparable shear and tensile strengths to the commercially available GRAS (generally regarded as safe) category polymers and higher than the other natural polymers such as sodium alginate and guar gum. Further, these strengths were increased with the increase in concentration but no considerable increase was observed after 15 minutes of contact time, irrespective of polymers studied. Strengthening of bioadhesion may be due to the formation of more number of secondary bonds as time progresses.

Adhesive cups were studied for their bio/mucoadhesive strengths by using the specially fabricated apparatus. Tensile, shear and peel strengths were calculated after five minutes of contact time. The apparatus used to determine the *in vitro* residence of the adhesive cups. Modified disintegration apparatus was used for the study. The results showed that the AC 17, AC 18, AC 19 and AC 22 formulations exhibited residence times of 4.98, 4.82 and 5.08 hours respectively, which are beyond the period required for the complete absorption of the drug. Adhesive cup formulations AC 17, AC 18, AC 19 and AC 22 that showed superior qualities in the above studies were selected for further studies.

Table 5 represents the various factors considered for the formulation of core tablets. Microcrystalline cellulose, one of the most used filler-binders in direct tablet compression due to its excellent binding properties and high dilution potential in direct compression formulations is used in the formulation. Mucoadhesive polymers at varying proportions were used to retard the release of drug to achieve sustained release.

Table. 2: Physical Parameters of Core Tablets.

F. C	Diameter (mm)	Thickness (mm)	Weight Variation (%)	Hardness (Kg/cm^2)	Friability (%)
PD 1	2.81	0.76	0.52	4.38 ± 0.63	0.81
PD 2	2.8	0.77	0.48	4.32 ± 0.22	0.53
PD 3	2.79	0.78	0.43	4.58 ± 0.24	0.46
PD 4	2.78	0.78	0.32	4.39± 0.51	0.62
AA 1	2.81	0.81	0.62	4.87 ± 0.24	0.41
AA 2	2.81	0.81	0.51	4.22 ± 0.31	0.43
AA 3	2.8	0.81	0.42	4.62 ± 0.12	0.67
AA 4	2.8	0.82	0.28	4.02 ± 0.44	0.84
AE 1	2.83	0.81	0..81	4.18 ± 0.24	0.21
AE 2	2.82	0.8	0.67	4.25 ± 0.58	0.34
AE 3	2.81	0.8	0.51	4.18 ± 0.63	0.22
AE 4	2.8	0.79	0.46	4.11 ± 0.27	0.21
PJ 1	2.82	0.81	0.86	4.27 ± 0.14	0.87
PJ 2	2.82	0.81	0.69	4.12 ± 0.44	0.61
PJ 3	2.81	0.8	0.58	4.42 ± 0.51	0.49
PJ 4	2.81	0.8	0.49	4.23 ± 0.39	0.44
HPMC 1	2.8	0.8	0.23	4.28 ± 0.44	0.32
HPMC 2	2.8	0.8	0.21	4.15 ± 0.68	0.22
HPMC 3	2.79	0.81	0.20	4.34 ± 0.24	0.27
HPMC 4	2.79	0.81	0.15	4.26 ± 0.51	0.32
CP 1	2.83	0.79	0.37	4.38 ± 0.63	0.81
CP 2	2.83	0.81	0.34	4.32 ± 0.22	0.53
CP 3	2.83	0.81	0.26	4.27 ± 0.14	0.46
CP 4	2.82	0.82	0.22	4.12 ± 0.44	0.62
SA. 1	2.84	0.83	0.94	2.67 ± 0.64	0.32
SA. 2	2.84	0.83	0.87	2.79 ± 0.52	0.22
SA. 3	2.82	0.82	0.76	2.92 ± 0.49	0.27
SA 4	2.82	0.82	0.64	2.61 ± 0.56	0.32
GG 1	2.83	0.83	0.87	2.77 ± 0.44	0.81
GG 2	2.83	0.82	0.81	3.11 ± 0.48	0.53
GG 3	2.83	0.81	0.76	4.02 ± 0.44	0.46
GG 4	2.81	0.81	0.71	4.18 ± 0.24	0.62

Represents the results of various evaluation procedures adopted for the evaluation of physicochemical properties of NBATs. The thickness of NBATs using the isolated material falls between 1.14 to 1.28 mm and weight between 32.8 to 39.8 mg, suggesting its suitability for ease of administration without any discomfort. Weight variation and drug content uniformity studies suggest uniform mixing, validation of manufacturing process and its reproducibility. Results such as percent friability (0.21 to 0.87%) and hardness (3.11 to 4.42 kg/cm^2) were found to be within the recommended values of Indian Pharmacopoeia.

Table. 3 Evaluation of NBATs.

F. C	Weight (mg)	Weig HT Variation (%)	Thickness (mm)	Fria Bili TY (%)	Hardness (kg/cm^2)	Cumulative % Diffused (n=6)
NBAT 1	33.8 ± 0.127	0.62	1.14 ± 0.02	0.87	3.11 ± 0.48	3.79 ± 2.29
NBAT 2	33.6 ± 0.246	0.83	1.17 ± 0.07	0.61	4.02 ± 0.44	3.68 ± 2.02
NBAT 3	34.3 ± 0.321	0.94	1.18 ± 0.05	0.49	4.18 ± 0.24	3.42 ± 1.64
NBAT 4	34.7 ± 0.271	0.86	1.18 ± 0.06	0.44	4.25 ± 0.58	3.26 ± 1.82
NBAT 5	36.5 ± 0.442	1.34	1.21 ± 0.09	0.32	4.18 ± 0.63	2.98 ± 0.33
NBAT 6	36.9 ± 0.642	1.13	1.22 ± 0.07	0.22	4.11 ± 0.27	2.68 ± 0.22
NBAT 7	37.4 ± 0.229	1.44	1.22 ± 0.03	0.27	4.27 ± 0.14	2.42 ± 0.37
NBAT 8	37.9 ± 0.525	1.61	1.23 ± 0.07	0.32	4.12 ± 0.44	1.87 ± 0.48
NBAT 9	38.2 ± 0.634	1.51	1.22 ± 0.06	0.81	4.42 ± 0.51	4.26 ± 0.17
NBAT 10	38.9 ± 0.826	1.78	1.23 ± 0.09	0.53	4.23 ± 0.39	3.82 ± 0.18
NBAT 11	39.4 ± 0.268	1.64	1.28 ± 0.07	0.46	4.28 ± 0.44	3.28 ± 0.32
NBAT 12	39.8 ± 0.427	1.43	1.26 ± 0.05	0.62	4.15 ± 0.68	3.07 ± 0.37
NBAT 13	34.8 ± 0.241	1.34	1.18 ± 0.04	0.41	4.34 ± 0.24	3.18 ± 0.22
NBAT 14	33.6 ± 0.279	1.22	1.18 ± 0.06	0.43	4.26 ± 0.51	2.26 ± 0.91
NBAT 15	33.2 ± 0.212	1.31	1.17 ± 0.04	0.67	4.38 ± 0.63	1.68 ± 0.67
NBAT 16	32.8 ± 0.211	1.36	1.17 ± 0.09	0.84	4.32 ± 0.22	1.15 ± 0.36
NBAT 17	35.9 ± 0.168	0.84	1.19 ± 0.03	0.21	4.58 ± 0.24	3.88 ± 0.71
NBAT 18	34.8 ± 0.227	0.34	1.18 ± 0.05	0.34	4.39± 0.51	3.27 ± 0.57
NBAT 19	34.3 ± 0.237	0.38	1.17 ± 0.04	0.22	4.87 ± 0.24	2.96 ± 0.34
NBAT 20	33.8 ± 0.228	0.34	1.11 ± 0.02	0.13	4.22 ± 0.31	2.11 ± 0.29
NBAT 21	39.7 ± 0.716	1.11	1.22 ± 0.05	0.38	4.62 ± 0.12	3.98 ± 0.42
NBAT 22	39.1 ± 0.346	1.71	1.21 ± 0.06	0.32	4.57 ± 0.24	2.67 ± 0.67
NBAT 23	38.8 ± 0.325	1.57	1.21 ± 0.03	0.27	4.11 ± 0.16	1.46 ± 0.53
NBAT 24	38.2 ± 0.289	1.42	1.20 ± 0.04	0.24	4.03 ± 0.11	0.94 ± 0.51
NBAT 25	37.8 ± 0.462	1.44	1.22 ± 0.09	1.86	2.18 ± 0.81	5.87 ± 0.92
NBAT 26	38.4 ± 0.527	1.45	1.22 ± 0.07	1.34	2.67 ± 0.64	4.63 ± 0.82
NBAT 27	39.0 ± 0.415	1.45	1.23 ± 0.06	1.09	2.79 ± 0.52	3.59 ± 0.57
NBAT 28	39.9 ± 0.349	1.46	1.24 ± 0.06	0.88	2.92 ± 0.49	3.17 ± 0.54
NBAT 29	32.8 ± 0.215	1.11	1.16 ± 0.06	2.41	2.61 ± 0.56	6.18 ± 2.68
NBAT 30	32.4 ± 0.211	1.02	1.15 ± 0.05	2.33	2.77 ± 0.44	3.64 ± 1.98
NBAT 31	32.0 ± 0.237	0.98	1.15 ± 0.03	2.31	2.83 ± 0.37	2.73 ± 3.27
NBAT 32	31.7± 0.166	0.76	1.15 ± 0.03	2.26	2.91 ± 0.79	2.34 ± 3.18

The kinetic parameters of *in vitro* dissolution studies. The zero order, first order, Higuchi diffusion, Korsmeyer – Peppas, and Hixon Crowell were plots were drawn as represented and the respective linearity equations were reported and the corresponding correlation coefficients were reported. Results suggest that the NBATs could release the drug following first order in formulations without the inclusion of mucoadhesive material in the core tablets, but followed Higuchi diffusion or Korsmeyer – Peppas patterns after the inclusion of the same. Further the rate of release was sustained as the proportion of mucoadhesive substance is increased irrespective of the materials used. *In vitro* dissolution studies with the mucoadhesive layer exposed to the dissolution medium are represented in Table 6 It was found that less than 4% of drug diffused through the backing layer in four hours of study compared to 5.87% in sodium alginate and 6.18% in guar gum. The results suggest that the mucoadhesive material under investigation has not allowed the drug to diffuse through its backing layer enabling unidirectional release pattern.

The human acceptability studies with placebo NBATs on male human volunteers. The observed parameters such as duration of stay of the dosage form, its intactness at the affixed site, duration of maintenance of its structural integrity, palatability, effect on salivary secretion, discomfort to talk due to swelling or stickiness, possible irritation during and after removal of dosage form and feeling of dryness, bitterness etc. Volunteer's responses suggest that the NBATs 3, 7, 11 and 15 were found to be convenient and possess acceptable qualities comparable to the commercial polymers. The histological studies conducted on excised porcine buccal mucosa. The photomicrographs suggest that considerable damage was not found after the administration of NBATs.

Drug Excipient Compatability Studies

FTIR: Figures represent the FTIR Spectra's of mucoadhesive polymers under investigation. Results suggest that Ranolazine has not undergone any unacceptable interactions with the mucoadhesive polymers isolated from the natural edible sources.

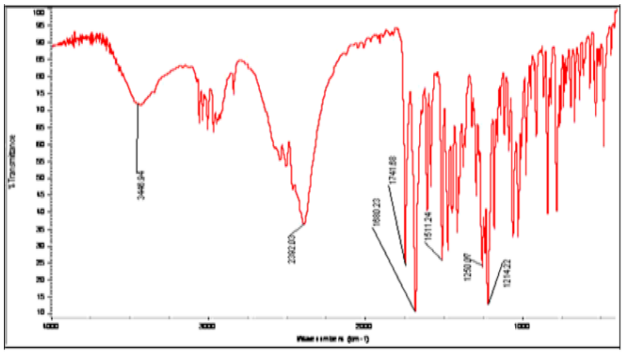

Figure. 1: FTIR Spectra of Ranolazine.

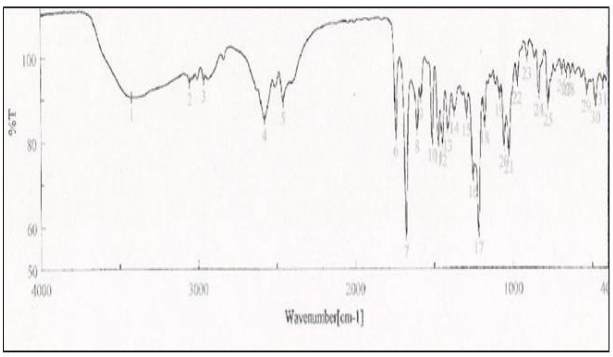

Figure. 2: FTIR Spectra of NBAT 14.

Differential Scanning Colorimetry

The DSC thermographs of Ranolazine and NBATs 3, 7, 11, and 14. The thermographs suggest that there are no significant interactions between the Ranolazine with the additives used in the formulation, thus the additives used and the methods adopted are acceptable.

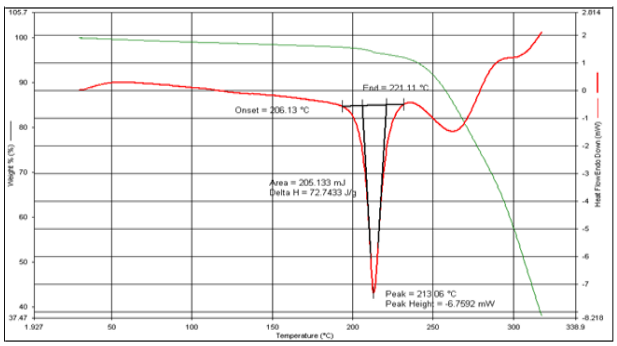

Figure. 3: DSC Thermograph of Ranolazine.

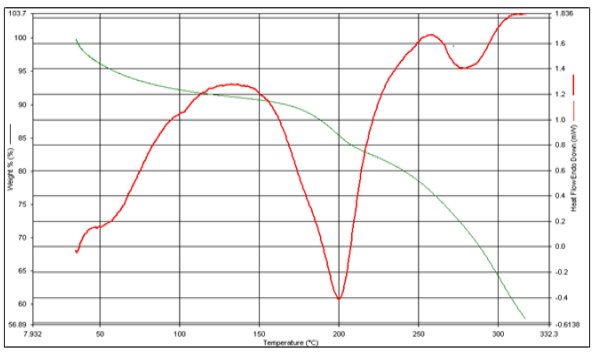

Figure. 4: DSC Thermograph of NBAT 14.

CONCLUSION

To present succinctly, it can be stated that the present investigation was carried out to develop a more effective non-invasive dosage form with maximum bioavailability that bypasses the hepatic first pass metabolism by delivering the drug unidirectional towards buccal mucosa. An additional investigation is the exploration of some mucoadhesive polymers from natural edible sources. The dosage form developed is expected to have better patient acceptability due to its unique ability of masking bitter taste. Biodegradability and biocompatibility are the additional advantages of these dosage forms. From these findings, it was evident that the natural mucoadhesive agents possess good handling properties and comparable bioadhesive strengths.

From all the results, the best possible combination possessing better characteristics were selected for the preparation of NBATs. Core tablets were prepared at varying proportions of drug to the polymer by direct compression technique. Finally NBATs were compressed after inserting suitable cores into cups manually.

REFERENCES

1. Y.W. Chien, Concepts and system design for rate-controlled drug delivery, in: Y.W. Chien Novel Drug Delivery Systems, Marcel Decker, Inc; New York., 1992; 2nd Ed,1-42.
2. M.J. Rathbone, G. Ponchel, F.A. Ghazali, Systemic oral mucosal drug delivery and delivery systems, Oral Mucosal Drug Delivery, Marcel Decker, New York., 1996; 74: 241-284.
3. Y. Sudhakar, K. Kuotsu, A.K. Bandyopadhyay, Buccal bioadhesive drug delivery-A promising option for orally less efficient drugs, J. Contr. Rel., 2006; 114(1): 15-40.
4. J. Hao, P.W.S. Heng, Buccal delivery systems, Drug Dev. Ind. Pharm, 2003; 29(8): 821-832.
5. P.L. Soo, L. Luo, D. Maysinger, A. Eisenberg, Incorporation and release of hydrophobic probes in biocompatible polycaprolactone- block-poly (ethylene oxide) micelles: Implications for drug delivery, Langmuir., 2002; 18: 9996-10004.
6. P. Perugini, I. Genta, B. Conti, T. Modena, F. Pavanetto, Periodontal delivery of ipriflavone: new chitosan/PLGA film delivery system for a lipophilic drug, Int. J. Pharm., 2003; 18: 1-9.
7. S. Senel, G. Ikinci, S. Kas, A. Yousefi-Rad, M.F. Sargon, A.A. Hıncal, Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery, Int. J. Pharm. 2000; 193: 197-203.
8. D. Tiwari, D. Goldman, R. Sause, P.L. Madan, Evaluation of Polyoxyethylene Homopolymers for Buccal Bioadhesive Drug Delivery Device Formulations, AAPS PharmSci., 1999; 1: 1-8.
9. R. Anders, H. Merckle, Evaluation of laminated mucoadhesive patches for buccal drug delivery, Int. J. Pharm, 1989; 49: 231-240.
10. R. Anders, H.P. Merckle, W. Schurr, R. Ziegler, Buccal absorption of Protirelin: an effective way to

stimulate Thyrotropin and Prolactin, J. Pharm. Sci.,1983; 72: 1481-1483.
11. J.H. Guo, Investigating the surface properties and bioadhesion of buccal patches, J. Pharm. Pharma col., 1994; 46: 647-650.
12. K. Danjo, H. Kato, A. Otsuka, K. Ushimaru, Fundamental study on the evaluation of strength of granular particles, Chem. Pharm. Bull, 1994; 42: 2598-2603.
13. M. Ishida, N. Nambu, T. Nagai, Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and carbopol, Chem. Pharm. Bull., 1982; 30: 980-984.
14. N.A. Nafee, F.A. Ismail, A. Nabila, Boraie, L.M. Mortada, Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, Int. J. Pharm., 2003; 264: 1-14.
15. T. Save, U.M. Shah, A.R. Ghamande, P. Venkatachalam, Comparative study of buccoadhesive formulations and sublingual capsules of nifedipine, J. Pharm. Pharmacol., 1994; 46(3): 192-195.
16. A.H. Shojaei, X. Li, Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethylether monomethacrylate, J. Control. Rel., 1997; 47: 151-161.
17. S. Miyazaki, A. Nakayama, M. Oda, M. Takada, D. Attwood, Chitosan and sodium alginate based bioadhesive tablets for intraoral drug delivery, Biol. Pharm. Bull., 1994; 17: 745-747.
18. C. Remunan-Lopez, A. Portero, J.L. Vila-Jato, M.J. Alonso, Design and evaluation of chitosan/ ethylcellulose mucoadhesive bilayered devices for buccal drug delivery, J. Control. Rel., 1998; 55: 143- 152.
19. B. Taylan, Y. Capan, O. Guven, S. Kes, A.A. Hincal, Design and evaluation of sustained release and buccal adhesive propronolol hydrochloride tablets, J. Control. Rel., 1996; 38(1): 11-20.
20. K.G.H. Desai , T.M.P. Kumar, Preparation and Evaluation of a Novel Buccal Adhesive System, AAPS Pharm. Sci. Tech., 2004; 5: 1-9.
21. B. Taylan, Y. Capan, O. Güven, S. Kes, A.A. Hincal, Design and evaluation of sustained-release and buccal adhesive propranolol hydrochloride tablets,J. Control. Rel., 1996; 38: 11-20. 22.
22. J.M. Labot, R.H. Manzo, A. Allemandi, Double layered Mucoadhesive Tablets Containing Nystatin, AAPS PharmSciTech., 2002; 3(3): 5-22.