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Design & evaluation of buccal tablets of drug loaded microspheres

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ABSTRACT

The purpose of this research is to formulate and evaluate in-vitro evaluation of Bucoadhesive tablets of Midazolam microspheres for the buccal delivery of the drug. Drug was presented in the form of microspheres to impart site specific drug delivery. Delivery of drug to the buccal cavity avoids first pass metabolism and comparatively reaches brain quickly. Microspheres can increase the site specific delivery system and possible to cross the body fluids like BBB, CSF, etc. Tablets were prepared by incorporating drug loaded microspheres and using bioadhesive polymers HPMC K15M and Carbopol 934. Micropheres were prepared by the Emulsion Cross linking method using Eudragit E100 and Eudragit RL100. Microsphres were characterized by SEM, FTIR, and particle size analysis and evaluated for percentage yield, drug loading, encapsulation efficiency and in vitro drug release. To achieve bioadhesion to the mucosal tissue, optimized microspheres were incorporated into bioadhesive tablets and were evaluated for in vitro drug release, in-vitro and in-vivo mucoadhesion. FTIR study showed that no chemical interaction occurred between the drug and polymers. Formulation F11 indicated a controlled in vitro drug release and good bioadhesive strength. The results indicated that this drug delivery system can be explored for controlled buccoadhesive drug release.

KEY WORDS: Midazolam, Microspheres, Emulsion and Buccal Tablets.

1. INTRODUCTION

Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety and improved patient compliance. Drug companies today are, therefore, engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast dispersing dosage forms, technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes.

Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000µm, they are made up of polymeric, waxy or other protective material, which are biodegradable synthetic polymers and modified natural products. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid, poly glycolic acid. Emulsion solvent, phase-separation method and spray drying method are commonly used for the preparation of microspheres. The success of any microencapsulation method depends on many factors such as the drug solubility, partition co-efficiency, polymer composition, molecular weight etc. Microspheres are formed by the evaporation of an organic solvent from dispersed oil droplets containing both polymer and drug. They have varied applications and are prepared using assorted polymers. However, the success of these microspheres is limited owing to their short residence time at the site of absorption.

2. MATERIALS AND METHOD

Materials: Midazolam was gifted by Brooks laboratories Ltd (India). Baddi H.P, Eudrajit E100, Eudrajit RL100, Span 80, Light liquid paraffin and Citric acid was gifted by Bafana pharmaceuticals. Chennai (India)

Pre formulation studies: Pre formulation studies were done for the selected drug candidate of Midazolam. Various organoleptic properties like colour, odour, physical appearance, Solubility, Melting point, Finding the maximum absorption and Compatibility studies were done.

Table.1. Preparation of Microspheres

Formulation	M1	M2	M3	M4	M5	M6	M7	M8	M9
Midazolam	10	10	10	10	10	10	10	10	10
Eudragit E 100	10	20	30	-	-	-	5	10	15
Eudragit RL 100	-	-	-	10	20	30	5	10	15
Citric acid	3	3	3	3	3	3	3	3	3
Distilled Water(ml)	10	10	10	10	10	10	10	10	10
Glutaraldehyde (25 % solution)	1	1	1	1	1	1	1	1	1
Light Liquid Paraffin (ml)	50	50	50	50	50	50	50	50	50

Evaluation of Microspheres: The morphology of the microspheres was determined by Scanning electran microscopy. Samples were examined under the Philips SEM 500 Scanning electron microscope. The percentage yields and Drug entrapment efficiency of different formulations were determined. Swelling Index was determined by measuring the extent of swelling of microspheres in phosphate buffer pH 5.5. The *in vitro* Buccoadhesive property of microspheres was evaluated by wash-off method by using freshly excised piece of goat buccal mucosa.

Release studies were carried out on all formulations in triplicate, employing a basket type Dissolution test apparatus- USP XXII. The withdrawn samples were filtered through a membrane filter (0.45µm) and were analysed for the drug content by spectrophotometrically at 216nm.

X-Ray Diffraction (XRD) Studies were carried out for Drug Midazolam, empty microspheres and Midazolam loaded microspheres.

Table.2. Formulation of buccoadhesive tablet

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Midazolam Loaded Microsphere	16	16	16	16	16	16	16	16	16	16	16	16
Carbopol 934 P	--	--	--	--	20	40	60	80	10	20	30	40
HPMC K15M	20	40	60	80	--	--	--	--	10	20	30	40
Calcium hydrogen Phosphate	20	20	20	20	20	20	20	20	20	20	20	20
Mannitol	89	69	49	29	89	69	49	29	89	69	49	29
Mg Stearate	5	5	5	5	5	5	5	5	5	5	5	5

Buccoahesive tablets containing Midazolam were prepared by direct compression technique using variable concentration of carbopol 934 P, HPMC K15M. The entire ingredients except magnesium stearate were blended uniformly, passed through sieve number 22. After sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 minutes, the tablet were compressed with 9mm punch. The weight of the tablets was kept constant for formulations F1 to F12.

Evaluation of buccoadhesive tablet: The prepared Buccoadhesive tablets were evaluated for Drug content, Bioadhesive strength and Swelling index. In-vitro release rate study of buccoadhesive tablet of Midazolam was carried out using the Apparatus 2 (Basket apparatus) method. Medium used for release rate study was 900ml phosphate buffer pH 5.5 during the course of study whole assembly was maintained at 37±0.5ºC. 5 milliliters of sample at one hour interval was withdrawn and analyzed.

The withdrawn samples were dilute with dissolution medium and then filter it with whattman filter paper and analysed at 216 nm. To find out the exact mechanism of drug release, the dissolution data of the optimized batch of buccoadhesive tablets were subjected to data fitting according to the Korsmeyer-Peppas equation, which describes drug release from a polymeric system.

Stability studies: In this study, stability study was done for at conditions like Room temp. (RT) and 40ºC & 75% RH. The samples were assayed for drug content at regular intervals for two weeks for the period of six months.

3. RESULTS AND DISCUSSION

The flow property of microspheres was studied by calculating the angle of repose (ɵ in degrees) and compressibility index (CI, %). The value of ɵ ranged from $22^{\circ}.77^{1}$ to $25^{\circ}.17^{1}$ indicating that the microspheres had good flow properties. The CI value was found to be in the range of 17.34±0.734 to 20.27± 0.47%, which also indicated good flow properties.

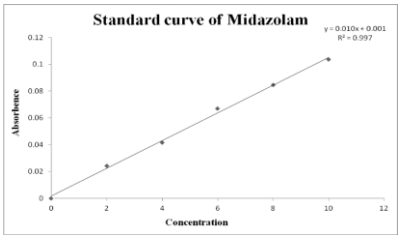

Figure.1. Standard curve of Midazolam

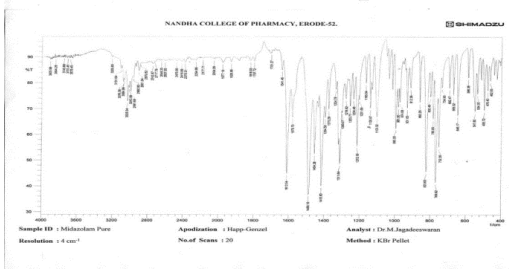

Figure.2. IR spectrum of midazolam (pure)

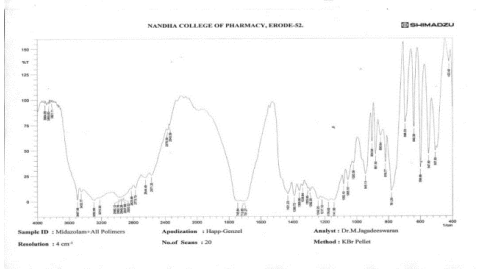

Figure.3. IR spectrum of midazolam+ all polymers

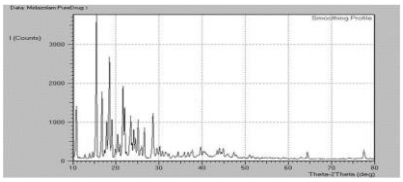

Figure.4. XRD Spectra of Midazolam-Pure Drug

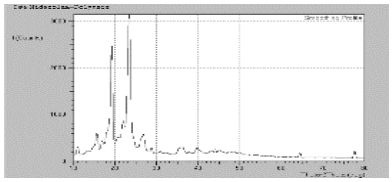

Figure.5. XRD Spectra of Drug Midazolam and Polymers

Particle size analysis: Results had shown that as the concentration of Eudragit RL100 and Eudragit E100 polymers increased, the size of the microspheres also increased. Amongst all nine batches of Microsphere, Batch M7 to M9 constantly increased in size while, Batches M1 to M6 shows relatively different in the size of microsphere. Batch M8 Microsphere containing Equal concentration of polymers produced optimum size of Microsphere.

Surface Morphology: SEM analysis shows that the images of the optimized batch M8 microsphere using equal concentration of Eudragit polymers have uniform and similar morphologies, being a spherical like shape. The Microspheres Produced by emulsion cross linking method, all batches have uniform and similar morphologies.

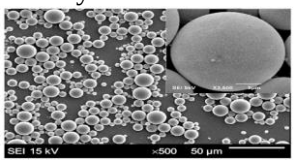

Figure.6. SEM Photograph of Formulation M8

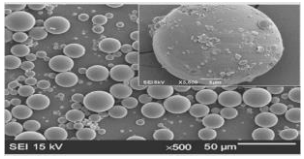

Figure.7. SEM Photograph of Formulation M9

Drug loading and encapsulation efficiency: From all 9 different batches, Batch M8 of equal composition of Eudragit E 100 and Eudragit RL100 polymers in the drug-polymer ratio of 1:2 shows better drug content and encapsulation efficiency, So that Batch M8 chosen for the Buccal tablet formulations. Encapsulation efficiency ranged from 82.79 to 93.74%. It was found that the encapsulation efficiency increased with increasing amounts of polymers in the microspheres. Formulations M8 and M9 showed a relatively higher encapsulation efficiency, these formulations contained a higher polymer concentration. It can be inferred from the results that there was a proper distribution of midazolam in the microspheres.

***In vitro* drug release studies:** The release profile of the drug from microspheres clearly indicates that the concentration of polymers slow the release of midazolam from microspheres. At the end of 12 hours, in vitro drug release from formulations M1 to M9 was found to be 83.1 to 98.9% in the buccal environment. The total cumulative quantity of the drug released at the end of the 12 h dissolution test was below 100% for all dosage forms. This may be in part due to the relatively slow release of entrapped drug from the matrices undergoing testing. Among various formulations, M8 was found to have a good release pattern and controlled release up to 12 hours. Hence, M8 was selected as the optimized formulation and incorporated in the preparation of the buccal tablets.

Bioadhesive Strength: The Bioadhesive property of Buccoadhesive tablets containing varying proportion of polymers was determined with a view to develop a good adhesiveness without any problems. The bioadhesion characteristics were affected by the type and concentration of the bioadhesive polymers. The highest adhesion force i.e. highest detachment force (38.48) was proposed by F11 containing HPMC and Carbopol 934.

F1 to F4 containing only HPMC and F5 to F8, containing only Carbopl 934, from Batch F9 to F12 containing HPMC and Carbopol 934 in varying concentration, Batch F11 with same concentration of both polymers showed, good bioadhesive strength. From the observation it was concluded that increasing the concentration of Carbopol 934 P in the formulation resulted in increased bioadhesion.

Table.3. Evaluation of buccoadhesive tablet

Batch no.	Weight Variation (mg)	Thickness (mm)	Friability (%)	Drug content uniformity	Hardness (kg/cm^2)
F1	150.1±4.02	2.61±0.078	0.62	99.76	6.85±0.45
F2	150.5±2.11	2.66±0.05	0.53	98.35	7.10±0.3
F3	150.83±4.10	2.60±0.05	0.64	97.13	6.70±0.40
F4	150.16±4.76	2.53±0.15	0.63	98.52	7.05±0.15
F5	150.5±2.10	2.62±0.05	0.44	99.85	6.60±1.0
F6	150.3±3.95	2.63±0.05	0.63	97.54	6.42±0.08
F7	149.2±3.22	2.70±0.15	0.61	99.62	6.50±0.7
F8	150.16±3.02	2.76±0.115	0.49	98.43	6.45±0.05
F9	149.5±2.40	2.53±0.052	0.52	99.51	6.15±0.05
F10	150.13±3.21	2.52±0.06	0.41	99.23	6.12±0.43
F11	150.57±2.12	2.54±0.07	0.47	98.25	6.18±0.58
F12	150.27±3.18	2.78±0.14	0.49	97.18	7.84±0.72

Table.4. Swelling Index of Tablets of Batch F1 to F12

Batch no.	Time (hrs)						
	0	1	2	3	4	5	6
F1	0	0.109	0.397	0.603	0.850	0.932	1.138
F2	0	0.116	0.222	0.475	0.644	0.855	0.981
F3	0	0.104	0.530	0.658	0.828	0.913	0.998
F4	0	0.155	0.568	0.672	0.734	0.858	0.899
F5	0	0.114	0.219	0.471	0.639	0.852	0.975
F6	0	0.118	0.221	0.478	0.645	0.856	0.979
F7	0	0.686	0.933	1.017	1.118	1.139	1.221
F8	0	0.597	0.802	0.927	1.007	1.130	1.171
F9	0	0.559	0.879	1.159	1.379	1.458	1.478
F10	0	0.548	0.789	1.116	1.275	1.308	1.386
F11	0	0.524	0.214	0.414	1.024	1.254	1.324
F12	0	0.571	0.147	1.106	1.124	1.171	1.278

***In-vitro* Dissolution Study:** All the formulations of prepared Buccoadhesive tablets of Midazolam microsphere were subjected to *in vitro* release studies, these studies were carried out using dissolution media of Phosphate buffer 5.5 pH. The release of midazolam from Buccoadhesive tablet varied according to the type and concentration of polymer. The cumulative % release of batch F1 to F4 were found to be 91.287% to 87.453% in 12 hrs respectively. From the result it was concluded that the increasing polymer concentration of HPMC, the release of drug might be slower which also supported by Xu and Sunada who reported that HPMC content was predominant controlling factor, as the concentration of polymer increased, drug release rates decreased and Vice Versa.

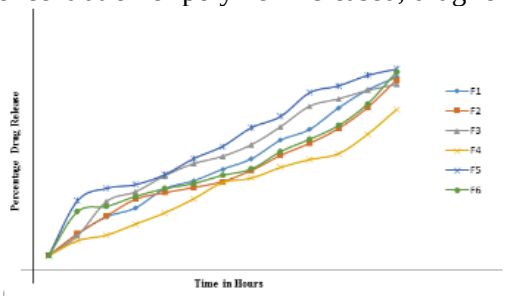

Figure.8. Dissolution profile of formulation F1 – F6

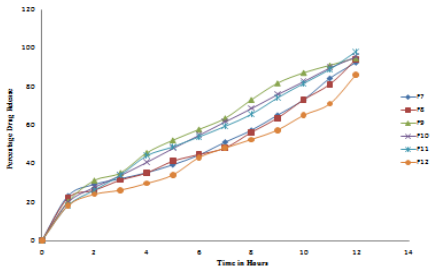

Figure.9. Dissolution profile of formulation F1 – F6

The cumulative % release of batch F5 to F8 were found to be 91.967 to 96.439% in 12 hrs respectively. From above observation it was concluded that carbopol polymer concentration increases duration of release increases.

The cumulative % release of batch F9 to F12 were found to be 89.795% to 98.643 % in 12 hrs respectively, The batch F11 contain Carbopol and HPMC K15M in 1:1 ratio, The cumulative % release of batch F11 was found to be 98.643% in 12 hrs, was concluded as best batch among the other formulations.

Kinetic Modeling: The results of in-vitro release studies were plotted in different model of data treatment as follows

a) Cumulative percent drug released v/s time (zero order rate kinetics)
b) Log cumulative percent drug retained v/s time (First Order rate Kinetics)
c) Cumulative percent drug released v/s square root of time (Higuchi's Classical Diffusion Equation)
d) Log of cumulative % release v/s log time (Peppas Exponential Equation)
e) (Percentage retained)$^{1/3}$ v/s time (Hixson –Crowell Erosion Equation)

Kinetic Modelling Data of Formulation F11

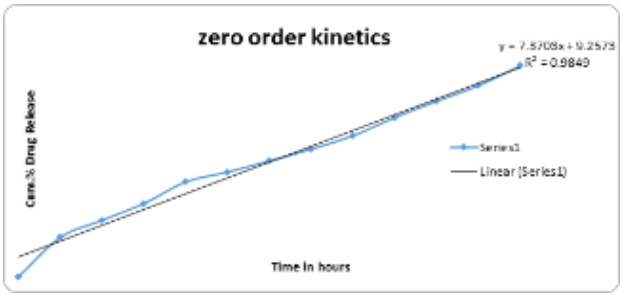

Figure.10. Kinetic profile Optimized formulation F11

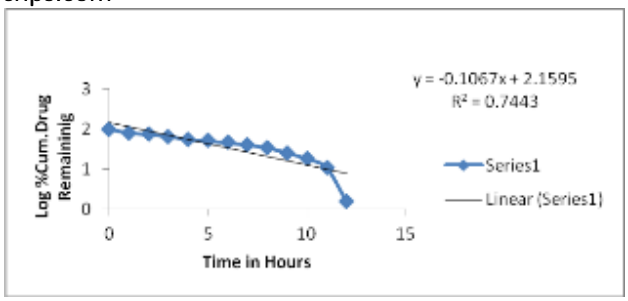

Figure.11. First order Kinetics

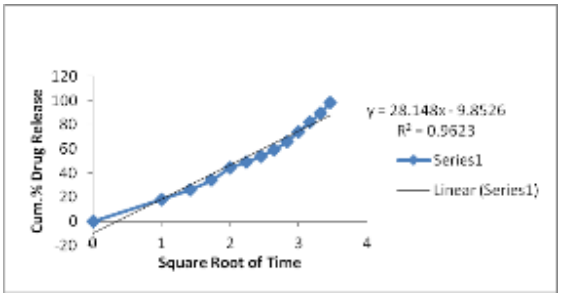

Figure.12. Higuchi Diffusion Model

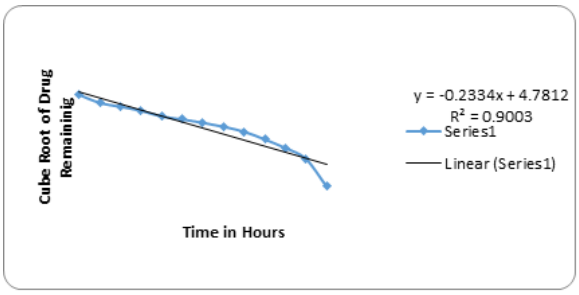

Figure.13. Hixson Crowell Model

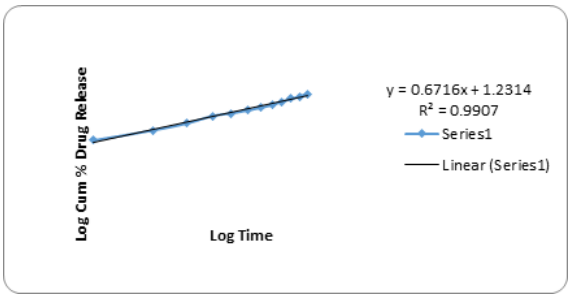

Figure.14. Korsmeyer Peppas Model

Table.5. Kinetic profile all the formulation

Code	Zero-order		First order		Higuchi		Hixon crowell		Peppas	
	R^2	slope	R^2	slope	R^2	slope	R^2	slope	R^2	N
F1	0.993	7.130	0.883	-0.071	0.921	26.53	0.941	-0.186	0.990	0.834
F2	0.969	6.338	0.812	-0.058	0.898	23.58	0.887	-0.158	0.970	0.759
F3	0.976	7.010	0.967	-0.070	0.965	26.93	0.986	-0.184	0.971	0.799
F4	0.986	5.636	0.919	-0.040	0.901	20.81	0.951	-0.121	0.982	0.937
F5	0.966	7.124	0.921	-0.092	0.961	27.45	0.964	-0.218	0.931	0.539
F6	0.943	6.145	0.734	-0.064	0.882	22.96	0.834	-0.164	0.88	0.553
F7	0.963	6.549	0.818	-0.072	0.916	24.68	0.895	-0.182	0.905	0.553
F8	0.964	6.573	0.766	-0.074	0.913	24.72	0.870	-0.184	0.919	0.576
F9	0.975	7.452	0.927	-0.099	0.977	28.81	0.977	-0.231	0.990	0.636
F10	0.986	7.379	0.874	-0.095	0.966	28.22	0.954	-0.224	0.985	0.650
F11	0.984	7.370	0.744	-0.106	0.962	28.14	0.900	-0.233	0.990	0.671
F12	0.971	6.060	0.851	-0.055	0.919	22.77	0.913	-0.150	0.933	0.614

Table.6. Kinetic profile all the formulation

Time (Hours)	% of drug Release	% of Cum Drug Remaining	Log % Cum Drug Remaining	Square root of Time	Log Time	Log % Cum Drug Release	Cube Root of % Drug Remaining
0	0	100	2	0	0	0	4.641589
1	18.348	81.652	1.911967	1	0	1.263589	4.338327
2	26.358	73.642	1.867126	1.414214	0.30103	1.420912	4.191555
3	34.183	65.817	1.818338	1.732051	0.477121	1.53381	4.037501
4	44.221	55.779	1.746471	2	0.60206	1.645629	3.820823
5	48.853	51.147	1.70882	2.236068	0.69897	1.688891	3.711989
6	54.026	45.974	1.662512	2.44949	0.778151	1.732603	3.582373
7	59.543	40.457	1.606994	2.645751	0.845098	1.774831	3.432927
8	65.8345	34.1655	1.533588	2.828427	0.90309	1.818454	3.24486
9	74.329	25.671	1.409443	3	0.954243	1.871158	2.949947
10	81.884	18.116	1.258062	3.162278	1	1.913199	2.626359
11	89.212	10.788	1.032941	3.316625	1.041393	1.950423	2.2096
12	98.435	1.565	0.194514	3.464102	1.079181	1.99315	1.161016

Stability studies: Stability study was carried out for the Formulation F11 by exposing it to different temperatures at Room temp. (RT) and 40ºC & 75% RH for six months. The samples were analyzed for content uniformity at regular

intervals of two weeks and it was evident that there was no remarkable change in the drug content of the prepared Buccal tablets. This indicated that the formulation F11 was stable at above mentioned temperatures. Stability studies showed mild changes in the surface characters and not affected by the drug content and encapsulation efficiency.

4. CONCLUTION

Development of bioadhesive buccal tablets of Midazolam is one of the alternative routes of administration to avoid first pass effect and provide prolonged release by increasing the diffusional path length using bioadhesive polymers. The emulsion crosslinking technique for the entrapment of Midazolam in Eudragit E 100 and Eudragit RL 100 produced a high yield of discrete microsphere with minimal agglomeration, reproducible drug loading efficiency and release profiles from batch to batch. The prepared microspheres showing good micromeritic properties with controlled drug release.

From the results, it was concluded that the in vitro drug release, bioadhesive studies, the formulation containing Carbopol 934 and HPMC K15M at the ratio of 1:1 is suitable for buccal delivery. The release pattern followed non-fickian diffusion with zero order release. Its possibility to avoid first pass metabolism of midazolam may ultimately show improvement of bioavailability than conventional oral dosage, probably as a consequence of prolonged residence at the absortion site.

Hence, It can be concluded from the results of present experimental work, that the Buccal tablets of Midazolam Microspheres are easy to administer, minimize the dose, reduce the side effects and improves the patient complaince and also midazolam might be a right and suitable candidate for oral controlled drug delivery via bucco adhesive tablets.

5. ACKNOWLEDGEMENTS

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