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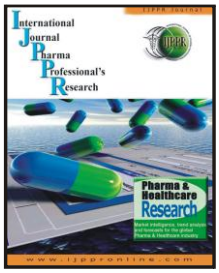

DEVELOPMENT AND *IN-VITRO* EVALUATION OF BUCCOADHESIVE FORMULATION OF DIMENHYDRINATE TABLET

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Abstract
Buccoadhesive tablets have long been employed to improve the bioavailability of drugs undergoing significant first pass hepatic metabolism. Dimenhydrinate is an anti-emetic drug. It was under goes extensive first pass metabolism resulting in an oral bioavailability of 46 % and it shows variable absorption from GIT. Buccal route offers several advantages such as rapid absorption, high plasma concentration level and ease of administration and termination of therapy. The present investigation concerns the development of Buccoadhesive tablets of Dimenhydrinate which were designed to prolong the buccal residence time after oral administration. Buccal tablets of Dimenhydrinate were formulated using four mucoadhesive polymers namely, Carbopol 934 P, HPMC K_4M, HPMC $K_{15}M$ and Sodium carboxymethylcellulose carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, Bioadhesive force and in vitro drug release. Formulation of F5 were formulated by using polymers Carbopol 934 P and Sodium carboxymethylcellulose provided controlled release of Dimenhydrinate over period of 8 hrs. The cumulative % of drug release of formulation F5 were 96.67. In-vitro releases of F1 to F9 were found to be diffusion controlled and followed zero order kinetics. The stability studies showed that there was no significant change in adhesive strength, in-vitro release when stored at room temperature, 40^oC, 2-8 ^oC for a period of 30 days. Formulation of F5 which were formulated by using polymers Carbopol 934 P and Sodium corboxymethylcellulose were established to be the optimum formulation with optimum bioadhesive force, swelling index & desired in-vitro drug release. Further investigations are needed to confirm the in-vivo efficiency, long term stability studies are needed to stabilize the controlled released (F5) formulations.

Keywords: - Buccoadhesive tablets, Dimenhydrinate ,Mucoadhesive polymers.

Introduction
The term 'buccoadhesive' describes materials that bind to the biological substrate, such as mucosal membranes. Adhesion of bioadhesive drug delivery devices to mucosal membrane lead to an increased drug concentration gradient at the absorption site and therefore improve bioavailability of systemically delivered drug[1]. Problem such as a high first pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity[2].Dimenhydrinate is a H_1 histamine antagonist. Antihistamines drug up the secretion of the nose, throat, and eyes. They relive itch and will help you go to sleep.

Dimenhydrinate prevents nausea, vomiting, or dizziness. However these drugs are not just antihistamine. They have a significant amount of anticholinergic activity[3].

Dimenhydrinate is unstable in gastrointestinal pH, after oral administration the absorbance of the drug is variable and undergoes extensive first pass metabolism, Bioavailability after oral administration is 46%. The onset of action is 60 min after administration and 10-20 min after I.V administration and half life is 1 to 5 hrs[4]. Hence it is suitable candidate for administration via the buccal route.

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The present study was an attempt to develop buccal muccoadhesive tablet of dimenhydrinate by using various polymers in various ratio which would provide sustained release in management in nausea and vomiting. The polymer were selected on the basis of their muccoadhesive performance, swelling nature of polymers namely carbopol 934 P, HPMC K_4M, Sodium carboxymethyl cellulose, HPMC $K_{15}M$ which would sustain the effect of drug for a period of 8 h[5-9].

Material and Methods

Dimenhydrinate was obtained from (Sigma – Aldrich Chemie Ltd, Chennai, Carbopol 934 P obtained from (Loba Chem. Pvt Ltd.), HPMC K4M and HPMC K15M was obtained (colorcon Asia Pvt Ltd.), Sodium CMC was obtained from (Reachem Lab Chemicals Pvt. Ltd.) All other Chemicals, either reagent or analytical grade, were used as received.

Preparation of Buccoadhesive Tablet formulation

The tablet were prepared using different combination of polymers as shown in Table No. 1, The various components in each formula were mixed by trituration in a glass pestle and mortar for 30 min the blended powder was then compressed using 8 mm diameter flat faced punch (Cad mach, single punch tablet compression machine) using a compression force of 5 tons and compression time of 15 seconds. The prepared tablets were 8 mm in diameter and 1.23 – 1.29 mm in thickness, each tablet weighted approximately 250 mg with a diameter of 8 mm[10].

Table 1: Compossition of Dimenhydrinate Buccoadhesive Tablets (mg/tab)

Sr. no.	Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Dimenhydrinate	50	50	50	50	50	50	50	50	50
2	Carbopol 934 P	30	120	30	120	30	120	60	60	30
3	HPMC K4M	120	30	---	---	---	---	15	40	20
4	HPMC K15M	---	---	120	30	---	---	15	40	20
5	Na CMC	---	---	---	---	120	30	60	10	80
6	MCC	43	43	43	43	43	43	43	43	43
7	Mg Stearate	5	5	5	5	5	5	5	5	5
8	Talc	2	2	2	2	2	2	2	2	2

*All the quantities are in mg.

Composition of formulation (F1 to F9) of Buccoadhesive tablets of Dimenhydrinate obtained adding different polymers in varieng ratio. i.e. 1:4 and 4:1 vice versa by direct compression method.

Tablet were evaluated for weight variation, hardness, friability and drug content uniformity. The hardness was determined using Monsanto hardness tester. The dimensional specification were measured using vernier calipers and friability test was performed by using Roche friabilator[11-13]. Weight variation test and test for content uniformity was conducted as per specification of USP 2000[14,15].

In vitro swelling Rate and Bioadhesion Studies

The swelling index of buccoadhesive tablet was evaluated using phosphate buffer pH 6.8 for each formulation one tablet were weighted and weight of tablet is denoted by (W_0) the tablet were placed in a beaker containing 200 ml of phosphate buffer pH 6.8 after each interval the tablet was removed from the beaker and weighted again up to 8 hour. The weight tablet after the removing from the medium denoted by W_1 and then swelling index was calculated using formula[16].

$$\% \text{ swelling index} = \frac{W_1 - W_0}{W_1} \times 100$$

Surface pH studies

The surface pH of the tablet was determined in order to investigate the possibility of any side effects on oral cavity. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH close to the natural pH.

The tablet were allowed to swell for 2 h in 1 ml of distilled water (pH 6.38±0.01). The surface pH was measured by a combined glass electrode was brought into contact with the tablets and pH was measured after 1 min equilibration. The method used was similar to that described by Battenberg [10].

In vitro Drug Release studies

The dissolution rates of manufactured buccoadhesive tablet were studied using the USP II rotating basket method at 37±0.5 ˚C and 50 rpm. Tablets containing 50 mg Dimenhydrinate were added to 900 ml of phosphate buffer pH 6.8. Sample were withdrawn at certain time interval and replaced with fresh dissolution medium. The amount of Dimenhydrinate release was determined by spectrophotometrically (UV- 1601) at 279 nm. The release rate study was carried out for 8 h[11-13].

Results

The evaluation studies of all tablet showed drug content, weight variation, friability and hardness as per the standard given in IP. Tablet with hardness between 6 to 8 kg were obtained with carbopol 934 P. Hardness increase with increases carbopol 934 P proportion in the formulation. Dissolution study revealed that hardness does not affect the release of drug from hydrophilic matrices.

Proper hydration of the tablet is important for good bioadhesion and drug release. The swelling values of the matrices with carbopol 934 P and other polymers like hydroxyl propyl methyl cellulose K_4M, $K_{15}M$ and sodium carboxy methyl cellulose showed increase in swelling value with increase percentage of carbopol 934 P in the formulation Table 2.

Table 2: Evaluation Parameters of buccal Formulations

Sr. No.	Formulation	Bioadhesive strength in g	% Water Uptake/ cm2 ±S.D	Surface pH ± S.D
1	F1	24.43	354.10±0.97	6.38±0.01
2	F2	37.59	297.51±1.56	6.39±0.005
3	F3	29.82	435.50±1.47	6.41±0.005
4	F4	38.48	178.33±0.90	6.40±.03
5	F5	28.65	378.12±1.13	6.38±.02
6	F6	33.62	268.24±0.95	6.41±.01
7	F7	21.51	342.31±1.15	6.38±.03
8	F8	37.38	302.16±1.12	6.37±.01
9	F9	20.14	350.36±1.64	6.42±.01

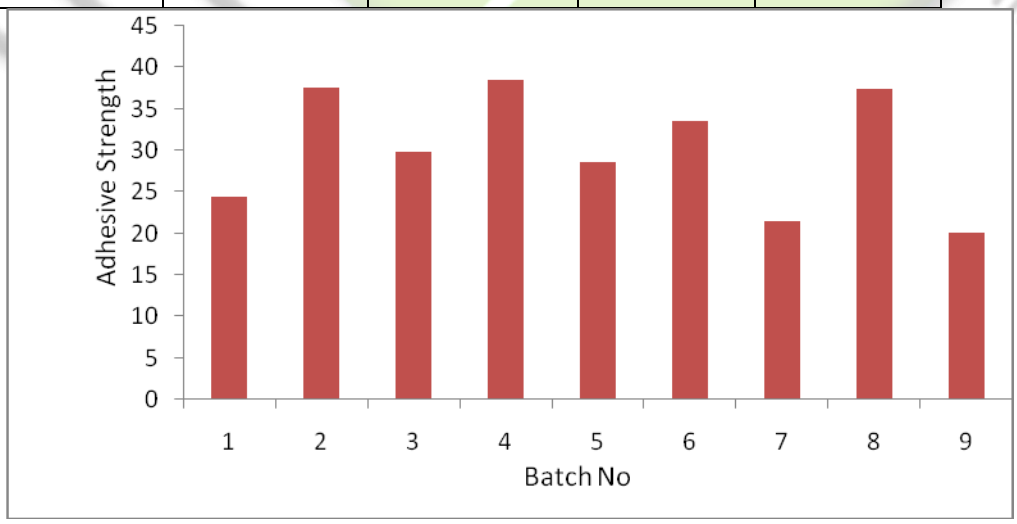

Fig. No. 1 :- Column graph of the adhesive force (gm)

Bioadhesion characteristics were affected by the type and ratio of the bioadhesion polymer. The highest detachment force was observed with formulation F2 prepared with maximum % of carbopol 934 P followed by F4 & F6

formulation.Increasing content of carbopol 934 P in the formulation resulted in bioadhesion.

Surface pH of all the formulation was found to be 6.38±0.01 (N= 3) which is very close to the buccal pH. Hence, these tablet should not cause any irritation to the buccal mucosa, table 2

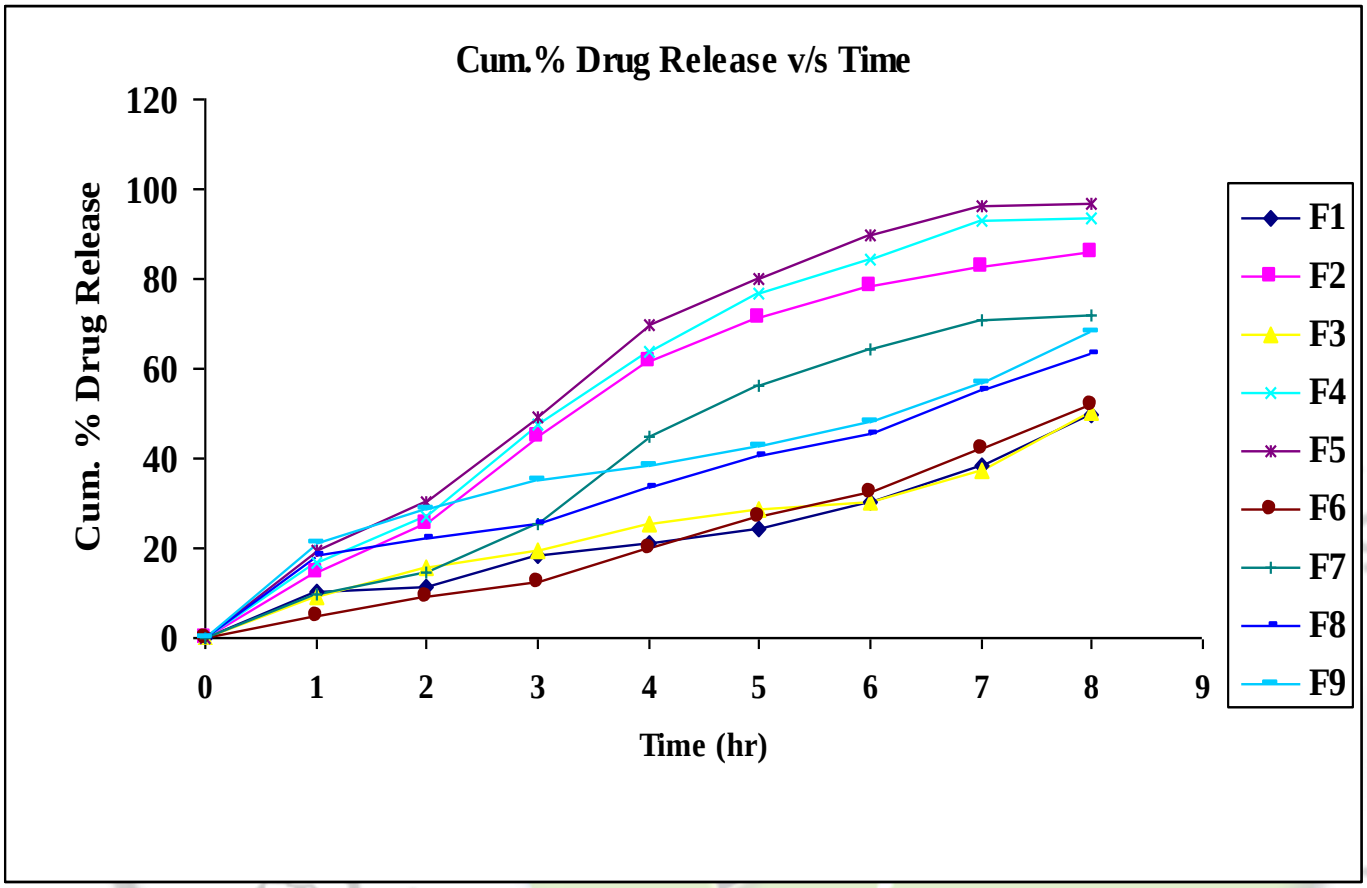

Fig No. 2 In vitro Cum. % Drug release v/s Time for formulation (F1 to F9) of Dimenhydrinate. (Zero Order rate)

The release of Dimenhydrinate from the buccal mucoadhesive tablet varied according to the type and ratio of the matrix – forming polymer Fig – 2 the release rate of Dimenhydrinate decrease with increasing concentration of hydroxyl propyl methyl cellulose K_4M and hydroxyl propyl methyl cellulose $K_{15}M$ but increase in the rate of release was found with increasing sodium carboxy methyl cellulose in-vitro i.e 96.67 % (N = 3 SD ± 1.23) carbopol 934 P is more hydrophilic than hydroxyl propyle methyl cellulose, so it swell rapidly. When we have decreased concentration, release rate of drug is also decreased as observed in F1 and F3 formulation.

Discussion

The present study was aimed to develop a buccoadhesive drug delivery system for delivery of dimenhydrinate. An attempt was made to formulate dimenhydrinate tablet using various muccoadhesive polymers in varying ratios.

The in-vitro drug release from carbopol 934 P and sodium carboxyl methyl cellulose in a ratio of 1:4 formulations F5 show maximum drug release in 8 h as compared to other polymeric ratios. The release of drug to be dependent on the nature and concentration of polymers used.

Evaluation for other properties of the formulation F5 is the best formulation as compared to other polymeric ratios. From the present study it can be concluded that the system will have better patient compliance because of the decrease in dose frequency as well as dose related side effects of dimenhydrinate like drowsiness, excitation, blurred or double vision.

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