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Formulation and Development of Buccal Drug Delivery System containing Curcumin

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Abstract: The main objective of this study was to improve the bioavailability of curcumin through buccal route. Curcumin is practically insoluble in water. After oral administration, most part of the drug was metabolized in liver. Therefore an attempt has been made to improve the bioavailability by using different conc. of sodium lauryl sulphate (0.1, 0.25 0.50 and 1 %) as bioenhancer. Buccal bilayer tablets were prepared by direct compression with different ratio of HPMC.K4M. (1, 2.5, 5, and 7.5%) as bioadhesive polymer and ethyl cellulose (10, 20, 30 and 40%) as backing layer. The formulation were characterized for physicochemical parameter such as weight variation, thickness, hardness, friability, mucoadhesive strength, drug content, swelling studies and *in vitro* diffusion studies. The best mucoadhesive performance and *in vitro* drug release profile were exhibited by tablets containing hydroxy propyl methyl cellulose K4M (5%) and sodium lauryl sulphate (0.1%). This product was more comfortable to the user due to absence of erosion, faster hydration rate and less viscosity of surrounding environment. To conclude that the formulated unidirectional, bilayered, buccoadhesive tablet for curcumin using HPMC as mucoadhesive agent is superior to oral conventional tablets, as it has the potential to bypass the first pass metabolism and improve the bioavailability of curcumin.
Key words: Curcumin, HPMC, Ethylcellulose, sodium lauryl sulphate.

INTRODUCTION

In the early 1980s, academic research groups working in the ophthalmic field pioneered the concept of mucoadhesion as a new strategy to improve the efficacy of various drug delivery systems. Since then the potential of mucoadhesive polymers was shown in ocular, nasal, vaginal and buccal drug delivery systems leading to a significantly prolonged residence time of sustained release delivery systems on these mucosal membranes. In addition, the development of oral mucoadhesive delivery systems was always of great interest as delivery systems capable of adhering to certain gastrointestinal (GI) segments would offer various advantages. With few exceptions however, mucoadhesive drug delivery systems have so far not reached their full potential in oral drug delivery, because the adhesion of drug delivery systems in the GI tract is in most cases insufficient to provide a prolonged residence time of delivery systems in the stomach or small intestine[1,2,3]. In the development of these drug delivery systems, mucoadhesion of the device is a key element. The term 'mucoadhesive' is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices[4]. Oral cavities are a novel site for drug delivery. The oral mucosa has been investigated in several studies as a means to give both local and systemic amounts of drug. Drug delivery across the oral mucosa, can be divided into three different types. ***Sublingual*** delivery, consisting of administration through the membrane of the ventral surface of the tongue and the floor of the mouth.

Buccal delivery**,** consisting of administration through the buccal mucosa, mainly composed of the lining of the cheeks and ***Local delivery*****,** consisting of administration through all areas other than former two regions[5]. The buccal cavity provides a highly vascular mucous membrane site for the administration of drug. The epithelial lining of the oral cavity differs both in type (keratinised and non-keratinised) and in thickness in different areas and the differences give rise to regional variation in permeability to drugs[6]. The main advantage of this buccal route is which Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs. **Improved patient compliance** due to the elimination of associated pain with injections, a relatively **rapid onset of action** can be achieved relative to the oral route.

EXPERIMENTAL (MATERIALS AND METHODS)

Curcumin was generously gifted by Natural remedies, Bangalore. HPMC K4M was gifted by signet chemical corporation, Mumbai. Sodium lauryl sulphate, Tween80, Mg.stearate and MCC were purchased from S.D fine chemicals. Mumbai.

PREPARATION OF GRANULES AND COMPRESSION OF BILAYERED TABLETS

The granules were prepared by wet granulation method and warm water was used as granulating agent for drug layer and hydro alcohol was used as granulating agent for backing layer. Accurately weighed quantities of the ingredients were mixed in a glass mortar and required quantity of granulating agent was added to the powdered mass and mixed thoroughly. The granules were prepared by passing the wet mass through British Standard Sieve (BSS) No.16. Wet granules were dried in hot air oven for 30 min at 60^{o}c and then passed through BBS No. 22. Finally, required quantity of the drug containing granules were placed on the precompressed backing layer and recompressed into tablets of 8 mm diameters. In each batch, 20 tablets were compressed.

STUDY ON THE EFFECT OF FORMULATION /PROCESS VARIABLES

The effect of formulation/process variables such as, backing layer thickness, drug to polymer ratio and the concentration of penetration enhancer on the physico-chemical and the *in vitro* drug release behavior were studied.

A. EFFECTS OF BACKING LAYER

Four different batches of curcumin buccoadhesive tablets were prepared corresponding to 10, 20, 30 and 40% ethyl cellulose backing layer keeping the following parameters constant,

- Concentration of penetration enhancer : 0.1% w/w SLS
- Concentration of polymer : 5% w/w

B. EFFECTS OF CONCENTRATION OF POLYMER

Four different batches of curcumin buccoadhesive tablets were prepared corresponding to 1, 2.5 ,5 ,and 7.5% polymer concentration keeping the following parameters constant,

- Backing layer : 13.5 mg ethyl cellulose
- Concentration of penetration enhancer : 0.1% w/w SLS

EVALUATION OF BUCCOADHESIVE TABLETS [8-20]

The prepared tablets were subjected for various quality control tests in order to characterize them.

A. AVERAGE WEIGHT AND WEIGHT VARIATION

The weight variation test of the tablets was done as per the guidelines of Indian Pharmacopoeia. Ten buccoadhesive tablets from each batch were weighed in sartorius digital balance and average weight was determined and standard deviation was calculated.

B. AVERAGE THICKNESS

The thickness of ten buccal tablets in each batch was determined using a digital vernier caliper. The average thickness and standard deviation was calculated.

C. HARDNESS

Hardness of the tablet is an indication of its strength. It is tested by measuring the force required to break the tablet across the diameter. The force is measured in kg/cm^2 and the hardness of about 4 kg/cm^2 is considered to be satisfactory for uncoated tablets. Tablet requires a certain amount of mechanical strength to withstand the shock of handling during its manufacture, packaging, shipping and dispensing.

D. FRIABILITY

Friability is the measure of a tablet's ability to with stands both shock and abrasion without crumbling during the handling of manufacturing, packing, shipping and consumer use. The weight of 10 tablets was noted and placed them in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a

plastic chamber, which revolves at 25 rpm, dropping the tablets a distance of 6 inches with the revolution. The pre-weighed tablet sample is removed after 100 revolutions, dusted and reweighed. Tablets that loose less than 0.5 to 1 percent in weight are generally considered acceptable.

Friability (%) =
Initial wt. of 10 tablets – final wt.of 10 tablets
---------- x 100
Initial weight of 10 tablets

E. DETERMINATION OF MUCOADHESIVE STRENGTH

Mucoadhesive strength is defined as the tensile force required breaking the adhesive bond between the model mucous membrane and the test polymer. It is important to assess its *in vivo* buccal residence time. In the present study, the mucoadhesive strength of formulated buccoadhesive tablets was evaluated using a modified physical balance.

E. DRUG CONTENT ESTIMATION

The Drug content of curcumin in the prepared buccoadhesive tablets was determined by UV spectrophotometry. From each batch 5 tablets were triturated to form fine powder after knowing the individual weight of each tablet. The powder equivalent to 100 mg of curcumin was weighed and transferred into a 100 ml volumetric flask and was dissolved in a mixture of phosphate buffer of pH 6.8 and 3% tween 80.The absorbance of this solution was measured at 426.02nm by using UV Visible spectrophotometer.

F. SWELLING STUDIES

The tablet was weighed accurately (w1) and placed in Petri dish containing 4 ml of phosphate buffer of ph 6.8. At the end of 2 hours, the tablets were removed from the Petri dish and excess surface water was removed carefully using filter paper and swollen tablets were reweighed (w2). The swelling index was calculated according to the formula:

Swelling index (%) = [(w2 – w1) /w1] x 100

G. *IN-VITRO* DIFFUSION STUDIES

Invitro permeation studies of buccal bilayered tablets were carried out in a franz diffusion cell containing using 50 ml of phosphate buffer, pH 6.8 with 3% tween 80 as medium maintained at 37 ± 1° C at 50 rpm for 8 hours with a simple modification. The prepared buccoadhesive tablet was placed by applying a moderate pressure onto a moistened membrane having a thickness of ~500um which is placed in the franz diffusion cell. At specified time interval, 5 ml samples were withdrawn and immediately replaced with equal volume of fresh buffer, which were later filtered diluted and assayed spectrophotometrically at 426.02 nm. The amount of curcumin release at each time interval was calculated from the absorbance of the samples. Dissolution studies were performed in three-sets and mean values were reported.

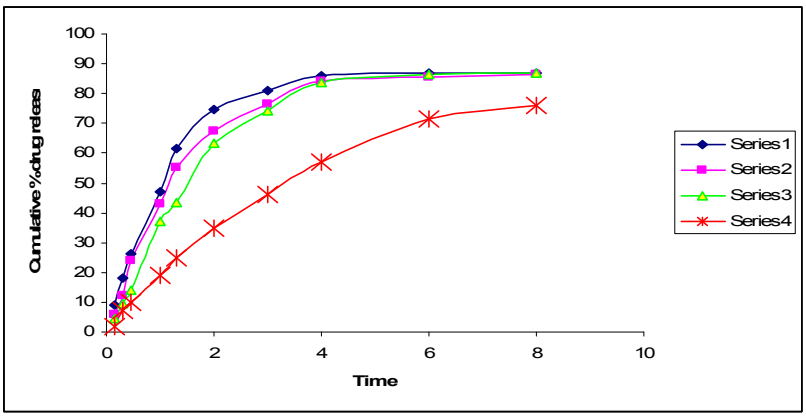
Table: 1 Physicochemical Evaluation of Various Polymer Concentrations Batches

S. No.	Evaluation	Concentration of polymer (%)			
		1	2.5	5	7.5
1	Average weight (mg)	150.527 ±0.501	150.710 ±0.397	150.849 ±0.454	150.821 ±0.565
2	Average thickness(mm)	1.999 ±0.035	2.021 ±0.012	2.031 ±0.028	2.056 ±0.036
3	Hardness (Kg/ cm^2)	3.149 ±0.098	3.339 ±0.159	3.615 ±0.014	3.787 ±0.067
4	Friability (%)	0.159 ±0.012	0.155 ±0.012	0.115 ±0.003	0.119 ±0.003
5	Mucoadhesive strength (g)	7.758 ±0.538	11.292 ±0.256	13.996 ±0.238	15.409 ±0.187
6	Drug content (%)	95.845 ±0.468	96.983 ±0.662	97.628 ±0.641	96.265 ±0.988
7	Swelling index (%)	68.615 ±2.050	70.642 ±0.630	76.672 ±1.265	81.728 ±1.835

Table.2 In vitro drug release pattern of various polymer concentrations batches

S. No	Polymer concentration (%)	Cumulative release (%) at different time intervals (h)										T_{50} Dissolution (h)
		0.15	0.30	0.45	1.00	1.30	2.00	3.00	4.00	6.00	8.00	
1	1	9.14	18.0	26.2	47.0	61.6	74.5	80.9	86.1	86.8	87.1	1.047
2	2.5	6.10	12.35	24.0	43.0	55.4	67.26	76.58	84.09	85.55	86.26	1.108
3	5	4.37	9.61	14.1	37.0	43.27	63.29	74.19	83.72	86.26	86.81	1.408
4	7.5	1.62	7.23	10.0	19.0	25.0	35.0	46.0	57.0	71.3	76.2	2.400

Fig.1 In vitro drug release pattern of various polymer concentrations batches



RESULTS AND DISCUSSION

FORMULATIONS AND EVALUATION OF UNIDIRECTIONAL, BILAYERED, BUCCOADHESIVE TABLET

Twenty batches of unidirectional, bilayered, buccoadhesive tablets, each containing 100 mg of curcumin were prepared by double compression technique. The influence of certain process / formulation variables namely backing layer, thickness and concentration of polymer on the physicochemical and *in vitro* drug release behavior was studied.

A. EFFECT OF BACKING LAYER

Average weight of buccoadhesive tablets prepared with 10, 20, 30 and 40% of backing layer were 131.321, 140.480, 149.906 and 150.418 mg respectively. This shows that increase in the backing layer thickness increases the average weight and all the values are in accordance with the theoretical values.

Backing layer thickness had no significant effect on dug content, swelling index and the mucoadhesive strength but Backing layer thickness had a significant effect on the *in vitro* drug release. Increase in the concentration of ethyl cellulose, retarded the drug release from the backing layer side, which become zero above 30% concentration.

There was no release from 30% and above ethyl cellulose containing batches over 8 hours period and therefore, it was selected to be an ideal backing layer, which is expected to prevent the drug escape into the buccal cavity and its subsequent entry into the portal vein.

B. EFFECT OF POLYMER CONCENTRATION

It was observed that increase in the concentration polymer increases the mucoadhesive strength of the buccal tablets. The maximum mucoadhesive strength was noted with 5% whereas it was minimum with 1%. The reason for higher mucoadhesion with higher HPMC content may be due to its capability to undergo extensive interpenetration with mucus layer.

The *in vitro* drug release studies of various batches with different concentration of polymer showed significant effect, an increase in polymer concentration reduced the drug release throughout. Based on the process / formulation variables studies, 30% ethyl cellulose as backing layer, 0.1%w/w concentration of penetration enhancers were selected

as ideal parameters. Even though various polymer batches showed differences in their *in vitro* drug release behavior.

All the above-mentioned batches were evaluated for average weight variation, average, thickness hardness, friability, mucoadhesive strength, drug content, swelling index are shown in Table - 1and *in vitro* drug release are shown in Table – 2 and fig – 1.

The study on these various process/formulation variables revealed that all the variables are important in developing a buccoadhesive tablet. A batch prepared with 5% polymer concentration, 0.1% penetration enhancer, with 30% backing layer was identified as ideal batch based on its optimum mucoadhesive strength of 13.99 g.

CONCLUSION

To conclude, that the batch prepared with 5% polymer concentration, 0.1% penetration enhancer, with 30% backing layer was identified as ideal batch based on its optimum mucoadhesive strength of 13.99 g. And the formulated unidirectional bilayered buccoadhesive tablet for curcumin using HPMC as mucoadhesive agent is superior to oral conventional tablets, as it has the potential to bypass the first pass metabolism and improve the bioavailability of curcumin. It is therefore expected to reduce adverse effect, cost and ultimately improve the patient compliance.

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