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Formulation and evaluation of mucoadhesive buccal tablets of montelukast sodium

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ABSTRACT

The objective of this study was to develop effective mucoadhesive buccal tablets of Montelukast sodium prepared by direct compression method using bioadhesive polymers like Xanthan gum, Tamarind gum and synthetic polymers like HPMC K15M, HPMC K100M and sodium CMC as a muco adhesive polymer. Buccal tablets were evaluated by different methods for parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, in vitro bioadhesive strength, in vitro drug release, stability studies in human saliva, in vivo mucoadhesive performance studies. Bioadhesion strength was increased with increase in the concentration of the polymer, higher bioadhesion strength was found in HPMC K100M. The tablets were evaluated for in vitro release in pH 6.8 phosphate buffer for 12 hr in standard dissolution apparatus. When compared with natural and synthetic polymers sustained drug release was found with synthetic polymer HPMC K100M(60mg) along with sodium CMC as a mucoadhesive polymer. The stability studies indicated that there was no significant change in drug release after 3 months.

Keywords: Montelukast sodium, Xanthan gum, Buccal tablets

INTRODUCTION

The concept of mucoadhesion was introduced in the field of controlled release drug delivery systems in the early 1980s [1,2] Thereafter, several researchers have focused on the investigations of

the interfacial phenomena of mucoadhesive hydrogels with the mucus. For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the

phenomenon is referred to as mucoadhesion. Hence a bacterial attachment is to tissue surfaces, and mucoadhesion can be modelled after the adherence of mucus on epithelial tissue. Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane.

Oral delivery involves the administration of the desired drug through the Oral mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of Oral tissues provides a much milder environment for drug absorption.[3] A number of relevant Mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1-5%), owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.[4]

MECHANISMS OF MUCOADHESION

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water.[5]

Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.[6] In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the

deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motions can contribute to this contact, but there is little evidence in the literature showing appropriate adhesion. Additionally, an undesirable adhesion in the oesophagus can occur. In these cases, mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (vander Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier.

In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Vander Waals and hydrogen bonds. [9] Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions. For example, molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induce its spread throughout the mucus layer, can present mucoadhesive properties.^[10]

ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS [7]

- Prolongs the residence time of the dosage form at the site of absorption.
- To avoid the first pass metabolism.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates.

- Drug is protected from degradation in the acidic environment in the GIT.
- Improved patient compliance and ease of drug administration.
- Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug.

Montelukast which is a selective antagonist of leukotriene receptors can be used to lower blood pressure and to treat asthma, allergic rhinitis, heart attack as well as arthritis (Wang *et al.*, 2017; Walia *et al.*, 2006). Montelukast is used as the sodium salt, but doses are expressed in terms of the base; Montelukast Sodium 10.37 mg is equivalent to about 10 mg of Montelukast and the bioavailability of Montelukast is almost 62% (Zhao *et al.*, 1997). Metabolism occurs through liver P450 (CYP) 3A4 and 2C8. Excretion happens almost exclusively in bile having a half-life from 2.7 to 5.5 hours in healthy adults. The pharmacokinetic profile is almost similar in females and males, young and adults. In patients with mild to moderate hepatic insufficiency, dosage adjustment is not required but data is insufficient regarding severe hepatic impairment. Montelukast and its metabolites are mainly excreted in bile and not urine, and it therefore has not been evaluated in patients having renal insufficiency. Hepatic first pass metabolism is the main drawback of conventional Montelukast Sodium and sustained release formulation of Montelukast Sodium is needed for that reason (Panchal *et al.*, 2012). Controlled or sustained release drug delivery systems have advantages as it reduces side effects, hepatic first pass effect and dosing frequency. Bioavailability enhancement and localized treatment can also be possible (Panchal *et al.*, 2012). Mucoadhesive drug delivery system using mucoadhesive polymers may be an effective way to sustain the drug release (Madgulkar *et al.*, 2008).

MATERIALS AND METHODS

Materials

Montelukast sodium was procured from Quest Pharma, Hyderabad, Na-Carboxy methyl cellulose, xanthan gum, Tamarind gum was purchased from B.M.R Chemicals, Hyderabad and HPMC K15M

and HPMC K100M were purchased from Loba Chemie Pvt Ltd, Mumbai, and other excipients were procured from spectrum pharma research solutions, Hyderabad.

PREPARATION OF MUCOADHESIVE BUCCAL TABLETS [8]

Mucoadhesive Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. drug was mixed manually with different polymers along with Sodium CMC as mucoadhesive polymers and mannitol as diluent for 10 min. The blend was mixed with Magnesium stearate for 3-5 min and then compressed into tablets by the direct compression method using 8mm flat faced punches. The tablets were compressed using a Cadmach rotary tablet machine.

EVALUATION OF FORMULATIONS [9-13]

Pre compression parameters

It includes Angle of repose, Bulk density, Tapped density, Carr's index, Hausner's ratio.

Pre compression parameters

It includes Weight variation, Hardness, Friability, Thickness and diameter, Drug content, *In-vitro* buoyancy studies, Swelling index and *In-vitro* dissolution studies.

RESULTS AND DISCUSSION

Mucoadhesive buccal tablets of Montelukast sodium were prepared by direct compression method, by using different natural and synthetic polymers like xanthan gum, Tamarind gum, HPMC K15M, and HPMC K100M in various ratios and Na-CMC as mucoadhesive polymer.

The prepared tablets were evaluated for various parameters such as compatibility studies, swelling studies, weight variation, hardness, drug content, thickness, friability, micro-environment pH, *in vitro* drug release studies, *in vitro* muco-adhesion strength and Release rate kinetics

From the results obtained from the FT-IR revealed that there was no chemical interaction

between the drug and the polymer used. The prepared tablets had good mucoadhesiveness.

Based on the dissolution studies of the Montelukast sodium mucoadhesive buccal tablets formulated by using direct compression method i.e., from F1-F12 maximum drug release was found in the F12 formulation containing HPMC K100M containing 60mg and Na-CMC as a backing layer.

So further drug release kinetics were performed for F12 formulation and the drug release was found to be zero order drug release with super case II mechanism.

Stability studies of the selected formulation was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies for formulations were carried out at 40 °C/75% RH for 90 days. There was no significant change in the drug release of the opti during the study period.

CONCLUSION

The main objective of the present study was to formulate and evaluate the controlled release muco

adhesive buccal tablets of Montelukast sodium by using xanthan gum, Tamarind gum, HPMC K15M, and HPMC K100M as polymers on the basis of their matrix forming properties and while Na-CMC as mucoadhesive polymer. The prepared tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, swelling studies, microenvironment pH, in vitro mucoadhesion strength, in vitro drug release studies and Release rate kinetics. Based on the in vitro mucoadhesion studies it was observed that the Increasing the polymer concentration caused an increase in the bioadhesive strength. Adhesion was reported to be affected by the hydration. Hydration of this mucoadhesive polymer is essential to initiate the mucoadhesive bonding process.

Based on the evaluation parameters it was concluded that the drug release, drug content and maximum swelling was found in formulation containing HPMC K100M (F12). So it was considered as the best formulation for formulating mucoadhesive buccal drug delivery.

Table 1: Formulation of Montelukast mucoadhesive buccal tablets by using natural polymers

Formulation	F25	F26	F27	F28	F29	F30
Montelukast	10	10	10	10	10	10
Na CMC	30	30	30	30	30	30
Xanthan gum	30	45	60	--	--	--
Tamarind gum	--	--	--	30	45	60
Mannitol	101	86	71	101	86	71
MCC	20	20	20	20	20	20
Aspartame	3	3	3	3	3	3
Mg ster	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total (mg)	200	200	200	200	200	200

Table 2: Formulation of Montelukast mucoadhesive buccal tablets by using synthetic polymers

Formulation	F31	F32	F33	F34	F35	F36
Montelukast	10	10	10	10	10	10
Na CMC	30	30	30	30	30	30
HPMC K15M	30	45	60	--	--	--
HPMC K100M	--	--	--	30	45	60
Mannitol	101	86	71	101	86	71
MCC	20	20	20	20	0	20

Aspartame	3	3	3	3	3	3
Mg ster	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total (mg)	200	200	200	200	200	200

Table 3: Precompression parameters & Post compression parameters

Parameters	Range	Parameters	Range
Angle of repose (θ) ±SD	23.12±0.28-25.46±0.32	Averagewt in (mg)±SD	199.7±0.24-200.6±0.38
Bulkdensity (gm/cm ³)±SD	0.202±0.46-0.224±0.21	Hardness(Kg/cm ²)±SD	4.16±0.02-4.85±0.08
Tappeddensity (gm/cm ³) ±SD	0.238±0.42-0.270±0.26	Diameter in (mm)±SD	7.99±0.68-8.14±0.24
Hausnerratio (HR)±SD	1.16±0.22-1.28±0.32	Thickness in (mm)±SD	2.16±0.52-2.54±0.26
Carr index (C.I) ±SD	14.75±0.35-22.22±0.18	Friability(%)±SD	0.22±0.16-0.58±0.14
		Drugcontent uniformity (%)±SD	98.16±0.32-99.68±0.42

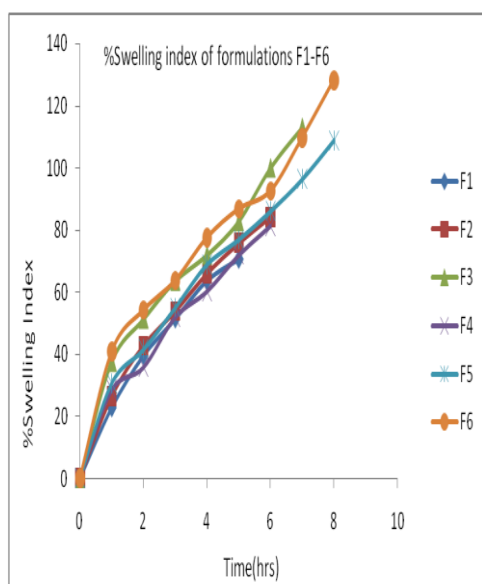


Fig 1:Swelling Index of F1-F6

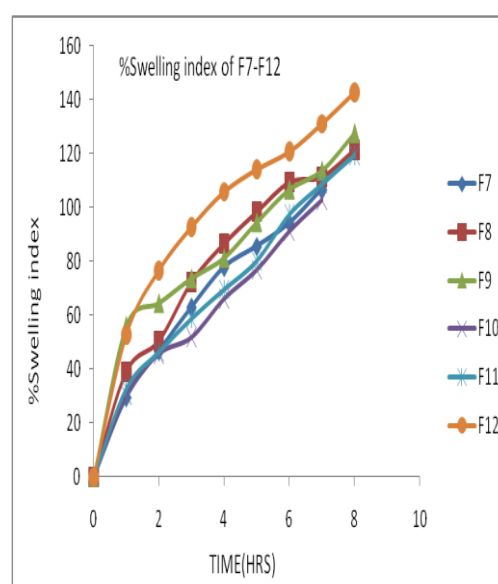


Fig 2: Swelling Index of F7-F12

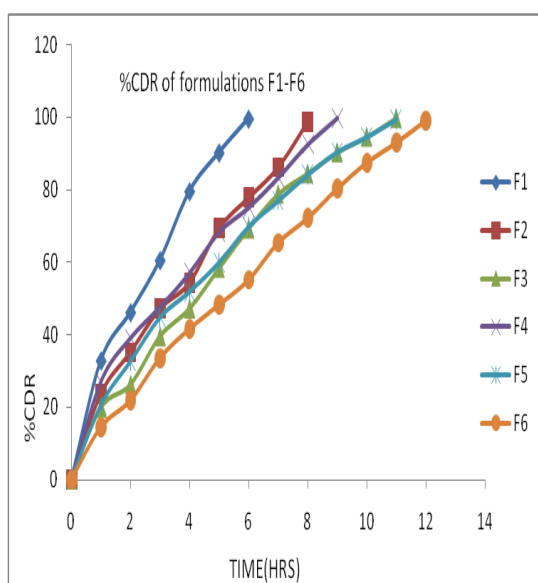


Fig 3: %CDR of F1-F6

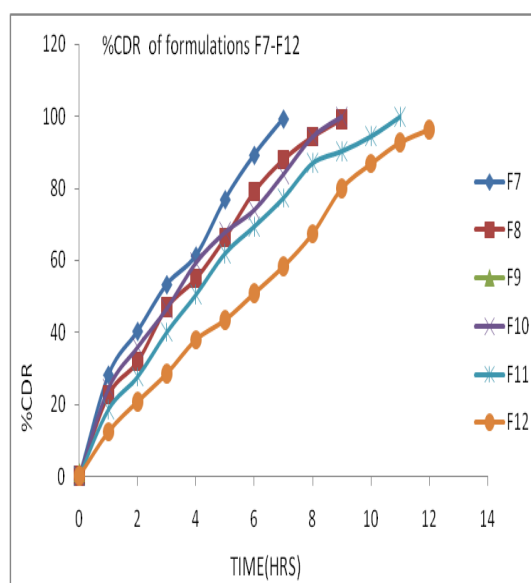


Fig 4: %CDR of F7-F12

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