Research Article

Design and Fabrication of Orodispersible Strip of Antiallergic Drug

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ABSTRACT

In present study, sodium alginate as film forming polymer and Sodium Starch Glycolate as a disintegrant with combination in different ratios could be promisingly used for the design of orodispersible strip of Montelukast sodium. Results obtained from F5 batch with acceptable in-vitro disintegration and *in-vitro* dissolution than other batches. Orodispersible strip of Montelukast sodium in strength of 10 mg was prepared by solvent casting method using sodium alginate, sodium starch glycolate, propylene glycol 400, sodium saccharine, menthol and Brilliant blue FCF. Compatibility study of Montelukast sodium was carried out with help of FTIR spectra. Retention of basic peaks of Montelukast sodium in FTIR spectra of physical mixture of API and excipient, concluding that there was no incompatibility with the selected excipients. The strips were characterized for drug content, thickness, weight variation, water absorption capacity, disintegration, in vitro drug release.

Keywords: Montelukast Sodium, sodium alginate, orodispersible strip, ethanol.

INTRODUCTION

The oral route remains preferred route for the administration of therapeutic agents due to low cost, ease of administration and high level of patient compliance. However, significant barriers are imposed on per oral administration of drugs, such as hepatic first pass metabolism and drug degradation within the gastrointestinal tract.[1]

To avoid the hepatic first pass metabolism and drug degradation within GIT; other routes such as nasal, rectal, vaginal, ocular, and oral cavity. Among these, oral cavity has an attracted particular attention, because it has a greater permeability.

Various formulations such as tablets, lozenges, chewing gums, sprays, films, patches, hydrogels, paste, ointments, solutions, microspheres etc. are developed for the delivery through the buccal mucosa.[2]

1.1 Advantages of fast dissolving films:

1. Ease of administration to podiatric, geriatric, bedridden and psychiatric patients who refuse to swallow tablet.

2. No need of water to swallow the disintegrating oral strips, which is highly convenient feature for patients who are travelling.

3. Rapid dissolution and absorption of drug, which may produce rapid onset of action.

4. Eliminate first pass metabolism so leads to increase bioavailability of drug.

1.2 Disadvantages of fast dissolving film:[3]

1. Drug with small dose requirement can only be administered.

2. Packaging of films requires special equipment.

3. Drugs which are unstable at buccal pH cannot be administered.

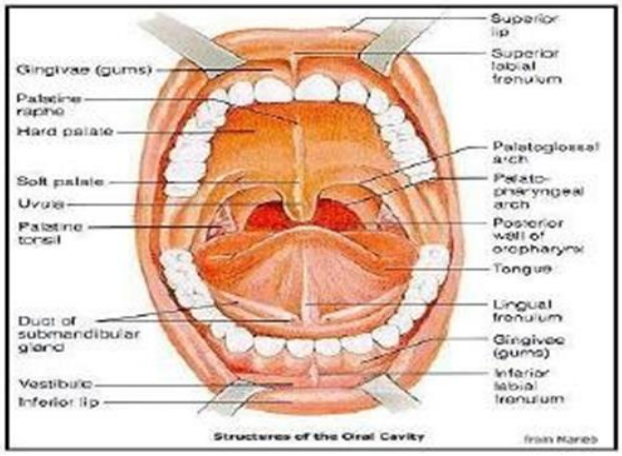

Figure 1: Structure of oral cavity

MATERIALS AND METHODS

Equipment's used in experiments:

Table 1: List of equipment's and its manufacturers

Equipment's	Manufacturers
Electronic Weighing balance	Shimazadu
pH meter	Thermo electron corporation
Magnetic stirrer	Remi
Sonicator	PCI, Mumbai
Multi-station tablet compression machine	Fluidpack
Heating Humidity Chamber	SECOR India
Vernier caliper scale	Mitutoyo

UV Spectrophotometer	Shimadzu Corporation
Dissolution test apparatus	Electrolab TDT 006
FTIR Spectrophotometer	Shimadzu Asia PacificPvt. Ltd

Chemicals and its suppliers:

Table 2: List of Chemicals and its suppliers:

Sr. No	Chemicals	Company
1.	Montelukast Sodium	Niksan Pharmachem, Surat,Gujrat.
2.	Sodium Alginate	Signet Chemical Corp.,
3.	Sodium Starch Glycolate	Loba Chemie.
4.	Propylene Glycol 400	Loba Chemie.

Estimation of Montelukast:

Ultra-Violet Spectroscopy

Ultra-violet Spectrum, electronic excitation occurs in the range from 200-800 mμ and involve the promotion of electron to the higher energy molecular orbital. It is very useful to measure the number of conjugate double bonds and also aromatic conjugation within the various molecules. It also distinguishes between conjugated and non-conjugated system[4].

Preparation of Stock solution

20 mg of Montelukast was accurately weighed and dissolved with Simulated Salivary Fluid pH 6.8 in 100 ml volumetric flask then the volume was made up to 100 ml with Simulated Salivary Fluid pH 6.8. This was 1st stock solution containing 200 µg/ml.

Determination of wavelength maxima (λ_{max}) of Montelukast

The solution of 10µg/ml in Simulated Salivary Fluid pH 6.8 was prepared and scanned in the range of 200-400 nm and wavelength maxima was determined by using Shimandzu U.V.Spectrophotometer.

Standard calibration curve of Montelukast:

Preparation of simulated salivary fluid pH 6.8

8.00 g of sodium chloride, 0.19 g of potassium phosphate monobasic and 2.38 g of sodium phosphate dibasic was dissolved in 1000 ml distilled water.

Preparation of standard calibration curve of Montelukast in simulated salivary fluid pH 6.8[5]:

From this 1st stock solution, 10 ml was pipette out and transferred in to a 100 ml volumetric flask and volume was made up to 100 ml with pH 6.8 phosphate buffer which contained the concentration of 20 µg/ml (2nd stock solution). From this solution, aliquots equivalent to 2-20 µg (1, 2, 3, 4, ------ 10 ml) were pipetted out into a series of 10 ml volumetric flask and volume was made up to 10ml with 6.8 phosphate buffer. The absorbance of these solutions was measured against the 6.8 phosphate buffer as blank at 330 nm using UV-Visible double beam spectrophotometer. Then a calibration curve was plotted taking concentration in µg/ml on X-axis and absorbance on Y-axis.

Solubility study[6]

The solubility of Montelukast was determined in solvents of different polarities. The solubility of Montelukast is usually determined by the equilibrium solubility method, which employs a saturated solution of Montelukast, obtained by adding an excess amount of Montelukast in the solvent to promote drug precipitation, and then stirring for 2 hr. until equilibrium was reached. The mixture was filtered and amount of Montelukast was determined by using UV Spectrophotometer at 330 nm.

Fourier Transform Infrared Spectroscopy[7]:

The samples were crushed with KBr to make pellets under hydraulic pressure of 10 tons, and then the FTIR spectra were recorded between 400 and 4000 cm-1. It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FTIR. FTIR spectral analysis of pure Montelukast and physical mixture of Montelukast, sodium alginate and sodium starch glycolate.

Formulation of rapidly disintegrating oral strips

Oral strips of Montelukast were prepared by using solvent casting method. Specified quantity of sodium alginate was weighed and dissolved in specified amount of water for overnight to get different % (w/v) solutions. Montelukast, sodium starch glycolate, propylene glycol and sodium saccharine were dissolved in specified amount of water in a beaker and dispersed in viscous polymeric mixture with continuous stirring using magnetic stirrer for 1 hour. Then colouring agent was added in resulting solution. Keep the solution aside for an hour to remove the air bubble the resultant mixture was poured into a borosilicate glass petri dish and allowed to dry at 50°C in hot air oven for 8 hrs. After complete drying, the film was removed from the plate and cut into the required size i.e. 2cm x 3cm= 6 cm^2. Oral strips were packed in aluminum foil. Different formulations designed.

Evaluation of oral strips:

Physical properties[8]

Thickness:

The thickness of each of 3 strips measured by micrometer screw gauge at different strategic locations. The average was determined.

Weight Variation:

For weight variation, individual weight of 6 strips of eachformulation was determined and the average weight was calculated.

Folding endurance:

The folding endurance was determined by repeatedly folding one strip at the same place till it broke or folded up to 300 times which is considered satisfactory to reveal good film properties. The numberof times the film could be folded at the same place without breaking gives the value of the folding endurance.

Water absorption capacity:

Water absorption capacity was determined by hydration study. Pre- weighed strips (*W0*) were placed on stainless steel wire mesh and deep in petri dish containing simulated salivary fluid for predetermined time and were taken out and wiped off to remove excess of surface water and weighed (*Wt*). Increase in weight of strip was determined at regular time intervals until constant weights was obtained and are calculated as shown in table.

$$\text{Water absorption capacity} = \frac{Wt - Wo}{Wo}$$

Where, *Wt* weight of strips at time t and *Wo* weight of strip at zero time.

Moisture content:

For moisture content, individual weight of 3 strips of each formulation was determined and placed in desiccators containing fused anhydrous calcium chloride. After 24 hours film was removed and weighed.

$$\% \text{ Moisture content} = \frac{Wo - Wt}{Wo} X\ 100$$

Where, Wo initial weight and Wt. final weight.

Disintegration time:

In-vitro disintegration time was determined by using disintegrating apparatus in simulated salivary fluid pH 6.8.the strip was placed in disintegrating apparatus; the disintegration time is the time when the film starts to break or disintegrates.

Drug content:

Drug content determination of the film was carried out by dissolving the film of 4 cm^2 in 100 ml of simulated salivary fluid pH 6.8 using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λ_{max} of 330 nm.

The results related various properties of prepared Montelukast strips were summarized.

***In-vitro* drug release:**

For *in-vitro* dissolution studies, each film was placed in a 900 ml of simulated salivary fluid pH 6.8, USP dissolution, apparatus II (Paddle), rotated at 50 rpm. The temperature of the dissolution media was maintained at 37±0.5°C. During the study, 5ml of aliquots were withdrawn at predetermined time interval and were replaced by fresh buffer. The amount of drug release in the media was determined by a UV-Visible Spectrophotometer at 330 nm.

Dissolution Kinetic Model[9]

Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected the dissolution profiles are evaluated depending on the derived model parameters. Result of kinetic treatment of dissolution studies were noted.

Differential Scanning Calorimetry (DSC) [10]

Thermal properties of the pure Montelukast and the physical mixture of drug and excipients were analyzed. The samples were heated in a hermetically sealed aluminum pan. Heat runs for each sample were set from 30 to 350°C at a heating rate of 10°C/ min, using nitrogen as blanket gas.

Stability study[11]

Stability study of an optimized formulation F5 were carried out by storing the strip (wrapping in aluminum foil) at 40±2°C and 75±5% relative humidity for 3 months. At an interval of 1 month, the strip was examined for any physical changes and *in-vitro* release study.

RESULTS

Identification test for Montelukast

Organoleptic properties:

The test was performed as per procedure given in material and method. The result is illustrated in Table 3.

Table 3: Tests and Observations

Tests	Observations	IP Specifications
Colour	White powder	Complies
Taste	Bitter	Complies
Odour	Unpleasant	Complies
Melting point	146°C-148°C	Complies

Determination of wavelength (λ_{max}) of Montelukast

The solution of 10µg/ml in Simulated Salivary Fluid pH 6.8 was prepared and scanned in the range of 200-400 nm and wavelength maxima was determined by using Shimandzu U.V. Spectrophotometer was found to be 330 nm.

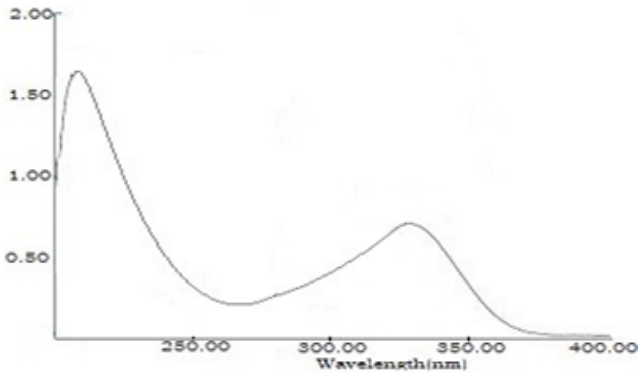

Figure 2: Scanning of Montelukast in Phosphate Buffer pH 6.8

Infrared absorption spectrophotometry

In present study, potassium bromide disc method was employed for pure drug and excipients Infrared (IR) studies. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum recorded.

Standard Calibration curve of Montelukast:

Table 4: Standard calibration curve of Montelukast in Phosphate Buffer pH 6.8

Concentration (µg/ml)	Absorbance
0	0
2.0	0.112±0.04
4.0	0.223±0.06
6.0	0.336±0.02
8.0	0.444±0.03
10.0	0.558±0.01
12.0	0.764±0.07
14.0	0.874±0.04
16.0	0.981±0.05
18.0	1.167±0.06
20.0	1.254±0.02

Solubility study of Montelukast in different solvents:

Solubility study of Montelukast was done in aqueous and non-aqueous media.

Table 5: Solubility study of Montelukast in different solvents

Sr. No.	Solvents	Solubility (mg/ml)
1.	Water	50.21
2.	pH 6.8 Phosphate Buffer	8.12
3.	Ethanol	55.42

Evaluation of oral disintegrating strips:

Physical properties

Table 6: Physical properties of prepared Montelukast strips

Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9
Parameters									
Thickness(mm)	0.05 ±0.02	0.08 ±0.01	0.07 ±0.02	0.06 ±0.02	0.08 ±0.01	0.08 ±0.01	0.07 ±0.02	0.08 ±0.01	0.09 ±0.01
Weight Variation (mg)	15.10 ±0.06	16.05 ±0.11	16.45 ±0.17	15.48 ±0.07	15.35 ±0.13	16.04 ±0.09	15.70 ±0.04	16.20 ±0.14	16.24 ±0.13
Folding endurance(Count)	>300	>300	>300	>300	>300	>300	>300	>300	>300
Water absorption capacity	396	411	406	399	408	399	389	392	408
% Moisture content	2.05 ±0.11	2.09 ±0.21	1.35 ±0.17	2.45 ±0.13	1.92 ±0.19	2.11 ±0.22	1.99 ±0.22	1.65 ±0.07	2.35 ±0.08
Disintegration Time (Sec)	14	15	13	12	12	14	16	15	13
Drug Content (%)	98.62 ±0.07	99.02 ±0.09	96.97 ±0.05	98.31 ±0.11	99.42 ±0.07	98.18 ±0.17	98.89 ±0.17	99.33 ±0.04	99.33 ±0.06

***In-vitro* drug release:**

Table 7: *In-vitro* drug release of oral strip formulation F1-F9

Time (Min)	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	18.28 ±0.24	17.08 ±0.11	16.15 ±0.09	28.35 ±0.17	33.92 ±0.18	31.31 ±0.02	26.38 ±0.04	24.23 ±0.06	16.92 ±0.15
1	54.78 ±0.14	52.56 ±0.19	45.32 ±0.19	62.62 ±0.04	66.28 ±0.25	64.67 ±0.09	53.03 ±0.14	51.39 ±0.17	50.05 ±0.19
1.5	66.61 ±0.25	65.88 ±0.06	59.26 ±0.18	68.39 ±0.17	73.06 ±0.14	69.63 ±0.23	68.40 ±0.27	67.01 ±0.25	65.24 ±0.09
2	74.23 ±0.16	73.49 ±0.19	73.45 ±0.31	75.98 ±0.32	82.47 ±0.11	80.05 ±0.02	78.47 ±0.10	76.90 ±0.15	74.21 ±0.20
2.5	79.09 ±0.11	76.89 ±0.24	74.37 ±0.07	79.02 ±0.18	85.72 ±0.16	83.27 ±0.14	84.79 ±0.22	82.86 ±0.31	80.16 ±0.28
3	86.48 ±0.19	89.25 ±0.33	88.08 ±0.06	87.02 ±0.24	90.13 ±0.31	88.72 ±0.09	87.09 ±0.17	86.49 ±0.05	84.73 ±0.24
3.5	91.66 ±0.09	92.54 ±0.25	90.88 ±0.05	93.24 ±0.27	96.27 ±0.06	94.67 ±0.04	89.62 ±0.32	89.08 ±0.19	86.25 ±0.25
4	96.43 ±0.25	95.65 ±0.09	94.54 ±0.11	97.55 ±0.14	99.72 ±0.04	98.81 ±0.12	92.35 ±0.21	91.49 ±0.27	89.74 ±0.33
4.5	99.31 ±0.08	98.93 ±0.11	98.67 ±0.06	-------	-------	-------	94.36 ±0.05	93.45 ±0.03	92.56 ±0.23
5	-------	-------	-------	-------	-------	-------	98.85 ±0.27	96.40 ±0.17	94.85 ±0.14

(Mean ± SD)

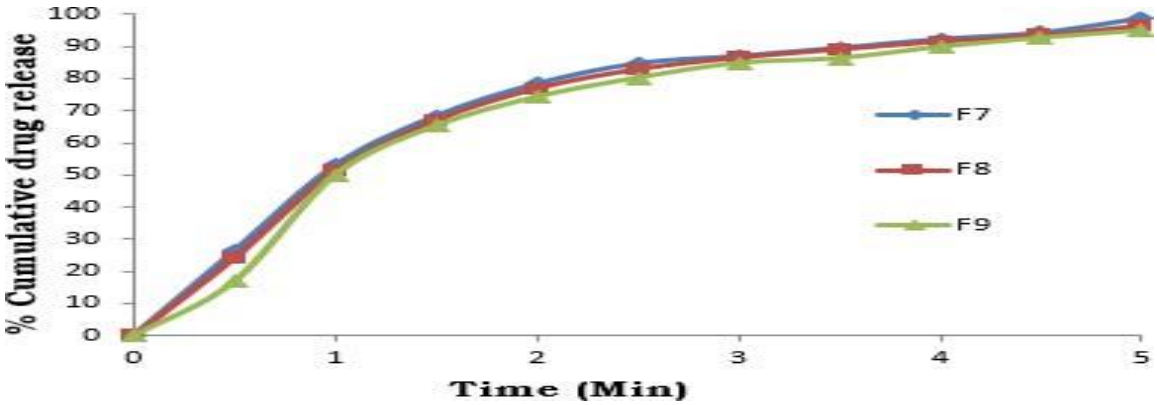

Figure 3: *In-vitro* release of oral strip formulation F7 – F9

DISCUSSION

Present study was carried with aim to design and fabricate orodispersible strip of Montelukast Sodium using varying concentration of film forming sodium alginate polymer and sodium starch glycolate as a disintegrant by solvent casting method.

Montelukast Sodium, procured sample was tested to confirm its identity by determining its colour, taste, odour, solubility, melting point and FT-IR studies. Montelukast Sodium is freely soluble in water and, ethanol and soluble in pH 6.8 Phosphate Buffer. The melting point of the drug was found to be 146-148^{0}C. These tests showing compliance with the Pharmacopoeial specifications of reference standard of drug Montelukast Sodium and was suitable for preparation of orally disintegrating strip.

CONCLUSION

In present study, sodium alginate as film forming polymer and Sodium Starch Glycolate as a disintegrant with combination in different ratios

could be promisingly used for the design of orodispersible strip of Montelukast sodium. Results obtained from F5 batch with acceptable *in-vitro* disintegration and *in-vitro* dissolution than other batches.

Moreover, F5 batch was found to be stable for a period of three months when kept at 40°C/75% RH.

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