INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUTION OF MONTELUKAST SODIUM ORAL THIN FLIMS

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ABSTRACT

The main objective of the study was to formulate and evaluate oral thin film containing drug Montelukast Sodium. The 4 and 5 % W/V HPMC, PVA, CMC films were prepared by Solvent Casting Method. Compatibility of Montelukast Sodium with polymers was confirmed by FT-IR studies. The presence of disintegrant showed a considerable effect on the disintegration time of the films. Montaleukast sodium can be prepared by solvent casting method. A 4% w/v of HPMC (fv) film exhibited required tensile strength, folding endurance and disintegration time. The drug release was about 98.5 % in 300 seconds(5 minutes). Hence, from the present investigation it can be concluded that oral thin film formulation can be a potential novel drug dosage form.

Key Words: oral thin film, Montelukast sodium, disintegration time

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INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia paatients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of Drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using superdisintegrations and hydrophilic ingredients. Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphagia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarted, uncooperative, nauseated or on reduced liquid intake/diets have

difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane[3]. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. Sublingual absorption is mostly rapid in action, but also short acting in duration Nitroglycerine, for example, is an effective antianginal drug but is extensively metabolized when taken orally (>90%). It is rapidly absorbed through the sublingual mucosa, and its peak plasma level is reached within 1-2 min. Because of its short biological half-life (3-5 min.), however the blood concentration of nitroglycerine declines rapidly to a level below the therapeutic concentration within 10-15 min. In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered (1-3). Sublingual products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia). Sublingual, meaning literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. There is considerable evidence that most sublingual substances are absorbed by simple diffusion; the sublingual area acting rather likes litmus paper, readily soaking up the substances. However, not all substances are permeable and accessible to oral mucosa.

Montelukast Sodium is a leukotriene receptor antagonist. Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours. Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.In vitro studies using human liver microsomes indicate that CYP3A4, 2C8, and 2C9 are involved in the metabolism of montelukast. At clinically relevant concentrations, 2C8 appears to play a major role in the metabolism of montelukast (4-6).

The main objective of the study was to formulate and evaluate oral thin film containing drug Montelukast Sodium.

MATERIALS AND METHOD

Calibration curve of Montelukast Sodium in 6.8pH phosphate buffer

By preparing the standard & stock solution we have found the absorbance of drug montelukast sodium was found to be measured at 282nm. From the standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made upto 10 ml with buffer so as to get concentration of 2, 4, 6, 8, 10 µg/ml. the absorbance of the solution were measured at 282 nm. This procedure was performed in triplicate to validate calibration curve.

Formulation Studies (7-9)

Oral Dissolving Films was prepared by using Solvent Casting Method. The specified amount of polymer(for viscosifying agent) was weighed and dissolved in specified amount of water for overnight to get a uniform dispersion of 4 % and 5 % (w/v) solution respectively. In another beaker specific amount of water is taken and add Drug, cross carmellose sodium, aspartame, citric acid and dissolve it. The drug

solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting Solution was degassed so as to remove any bubbles formed.The bubble free solution was casted on to a petri dish of surface area 28.6 cm^2. It was dried for 24 hours at room temperature. The film was removed from the petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Film of area 2.25 cm^2(1.25 X 1.25) was cut and stored in a butter paper covered with aluminum foil and stored in a desiccator. Formulation trials were taken by selecting three different water soluble polymers HydroxyPropyl Methyl Cellulose (15cps), Polyvinyl alcohol, Carboxy methyl cellulose. By varying the polymer ratio too we are going to optimize the final formula. The compositions of various trials are as mentioned in table-1.

Table-1 Composition of various oral thin film formulation trials

S No	Ingredients	F1 (mg/unit)	F2 (mg/unit)	F3 (mg/unit)	F4 (mg/unit)	F5 (mg/unit)	F6 (mg/unit)
1	Montelukast Sodium	25	25	25	25	25	25
2	CMC*	4	5	-	-	-	-
3	PVA*	-	-	4	5	-	-
4	HPMC* (15cps)	-	-	-	-	4	5
6	CCS	2	2	2	2	2	2
7	PEG**	20	20	20	20	20	20
8	Aspartame	1	0.5	1	0.5	1	0.5
9	Sodium saccharine	1	0.5	1	0.5	1	0.5
10	Water	Qs	Qs	Qs	Qs	Qs	Qs
Total weight		53	53	53	53	53	53

Note- * = Expressed as %w/v, ** = Expressed as %w/w of the polymer

RESULTS AND DISCUSSION

Calibration curve of Montelukast sodium in 6.8 phosphate buffer

From the standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made upto 10 ml with buffer so as to get concentration of 2, 4, 6, 8, 10 µg/ml. the absorbance of the solution were measured at 282 nm (Table-1). This procedure was performed in triplicate to validate calibration curve. A calibration curve was plotted (Fig-1).

Table-2 calibration curve plot

S.No	Concentration in µg/ml	Absorbance
1	0	0
2	2	0.015
3	4	0.040
4	6	0.058
5	8	0.076
6	10	0.099

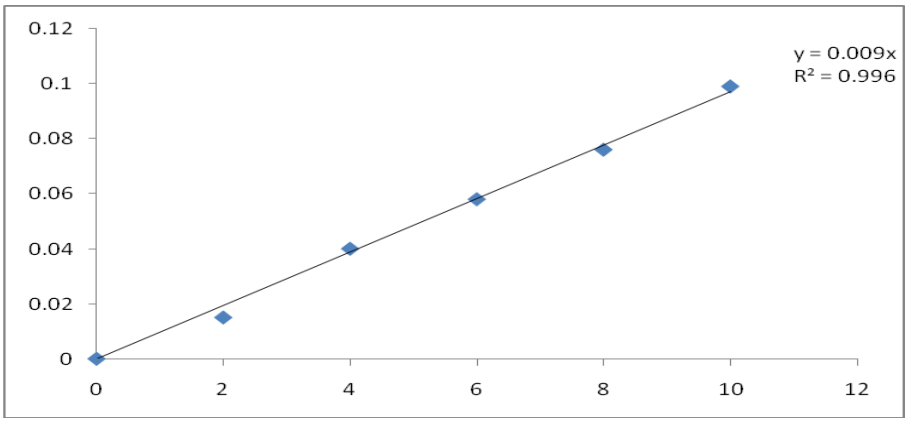

Fig-1 Calibration curve plot of Montelukast sodium in 6.8 phosphate buffer

Scanning Electron Microscopy (SEM)

Morphology of FDF is studied by SEM. The electron microscopy showed that all the two optimized formulations drug + HPMC + SSG are clear, colorless with smooth surface and little pores, without any scratches on the films (Fig- 2 and 3).

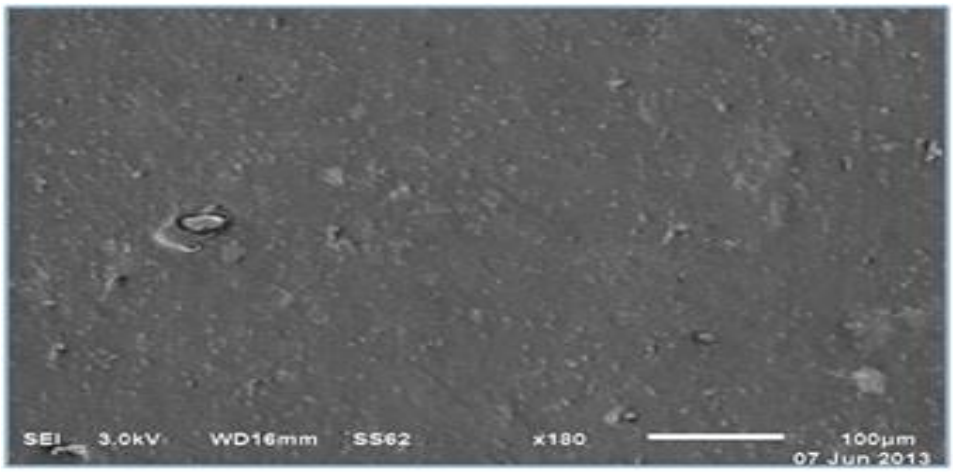

Fig-2 SEM of Drug + HPMC + SSG Formulation FA3

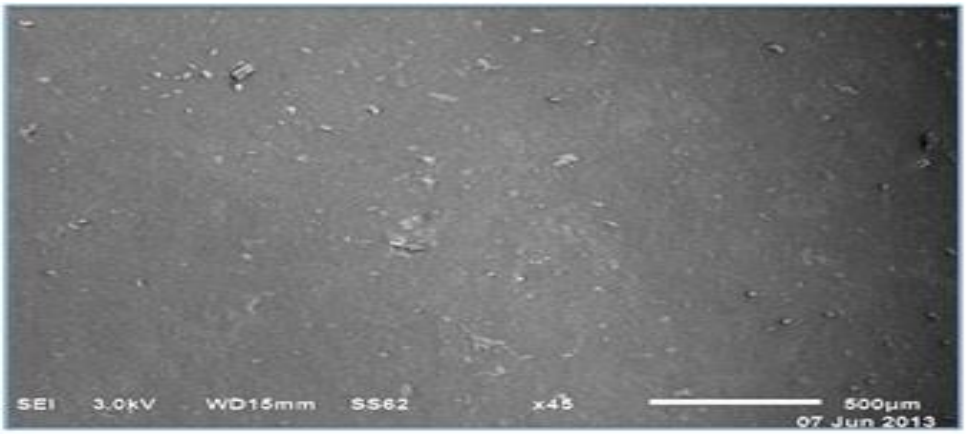

Fig-3 SEM of Drug + HPMC + SSG Formulation FA4

Formulation of oral thin films

Oral thin films containing Montelukast sodium were prepared by Solvent casting method. The films of HPMC, CMC and PVA (low viscosity) were prepared with an objective to dissolve the film in the mouth (Fig-4-7). 4 and 5 % w/v each of HPMC, CMC and PVA films were exhibited desired mouth dissolving time and other film parameters, compared to 2 and 3 % w/v of HPMC, CMCand PVA films which were difficult to remove and having low strength and exhibited unacceptable mouth dissolving time. Hence 4 and 5 % w/v of HPMC, CMC and PVA films were used for the study. Propylene glycol (20 % w/w of polymer) was used as plasticizer and to enhance the tensile strength of film.2 % cross carmellose sodium is used as disintegrant to dissolve the films rapidly when comes in contact with saliva. 1 % w/w Sodium saccharine was used as a sweetener and 1 % w/w of aspartame was used as flavoring agent.

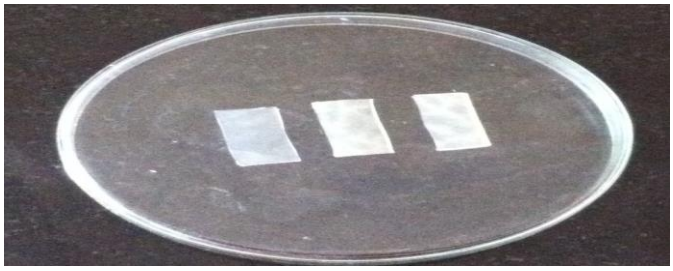

Fig-4 Oral thin film of HPMC

Fig-5 Oral thin film of Hydroxy propyl methyl cellulose

Fig-6 Oral thin film ofCarboxy methyl cellulose

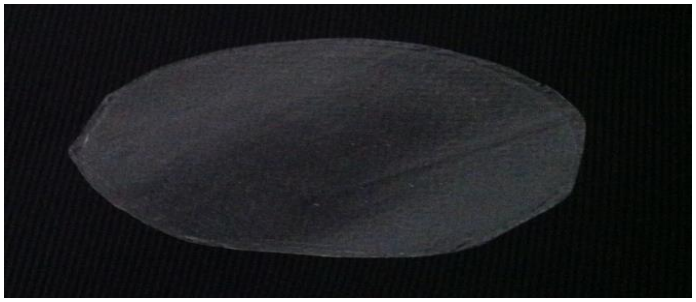

Fig-7 Oral thin film of Poly vinyl alcohol

In-vitro **dissolution**

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 500 ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5^0C at 50 rpm. 5 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37 ± 0.5^0C. Montelukast sodium in the samples was then determined spectrophotometrically at λmax of 282 nm. The results were expressed in table-3.

Table-3 Comparative evaluation of *Invitro*dissolution profiles of oral thin Films

SNO	Time in min	Cumulative % of drug release					
		FI	FII	FIII	FIV	FV	FVI
1	2	26 %	22.6%	22%	21%	45%	41%
2	4	53.3%	45.9%	49.3%	39.8%	77.3%	69.3%
3	6	78.3%	71%	69%	56%	98.5%	90.9%
4	8	93.2%	85.3%	80%	81%	98.5%	96.8%
5	10	96.3%	92%	92.4%	92.4%	98.5%	96.8%
6	12	97.3%	93.9%	94.5%	96%	98.5%	96.8%
7	14	98.4%	94.9%	97%	97.3%	98.5%	96.8%
8	16	98.6%	96.1%	97%	98%	98.5%	96.8%
9	18	98.6%	97.2%	97%	98%	98.5%	96.8%
10	20	98.6%	98	97%	98%	98.5%	96.8%

Stability Studies

The stability studies of the optimized batch F5 was carried out at 40°C/75%RH, 30/75%RH and 25°C/40%RH. These films were found to be unacceptable. Films stored at 40°C/75%RH were highly unstable within 1 month storage. Films stored at 25°C/60%RH were unstable after 2 months period by developing color change (slight yellow) and becoming sticky in appearance. Films stored at 25°C/40%RH were found to be stable for 3 months. The batch was found be acceptable visually, mechanically, with slight change in in-vitro disintegration time 30sec. The above observations indicate that temperature and humidity plays a critical role in the stability of the rapidly dissolving films containing HPMC as the film forming polymer. Therefore, precautions would be required during packaging and selection of packaging container would play a crucial role for stability of the Oral thin films. The promising formulations were subjected to short term stability studies. The formulations FA3 and FA4 were selected and were stored at 40°C/75%RH and tested for three month. The films were again analyzed for the Surface pH, drug content uniformity and disintegration time. The increase in the disintegration time was observed.

CONCLUSION

The main objective of the study was to formulate and evaluate oral thin film containing drug Montelukast Sodium. The 4 and 5 % W/V HPMC, PVA, CMC films were prepared by Solvent Casting Method. Compatibility of Montelukast Sodium with polymers was confirmed by FT-IR studies. Films were evaluated for weight variation and thickness showed satisfactory results. Tensile strength and folding endurance of the films were increased with increase in the concentration of polymer due to increase in the elasticity nature of the polymer. Disintegration time of the films were increased with increase in the concentration of the polymer, as more fluid is required to wet the film in the mouth. The presence of disintegrant showed a considerable effect on the disintegration time of the films. Content uniformity study showed that the drug is uniformly distributed in the film. No differences were observed in *in-vitro* dissolution of drug from the formulation trials I-VI as the film instantly gets wet by dissolution medium. Present study reveals that all the formulated films showed satisfactory film parameters. It can be concluded that, oral thin film-containing Montaleukast sodium can be prepared by solvent casting method. A 4% w/v of HPMC (fv) film exhibited required tensile

strength, folding endurance and disintegration time. The drug release was about 98.5 % in 300 seconds (5 minutes). The accelerated stability studies of the optimized f5 formulation indicates that the formulated oral thin films were unaffected after 3 months storage under accelerated conditions as there were no signs of visually distinguishable changes in appearance, disintegration time and cumulative percentage of drug release. Hence, from the present investigation it can be concluded that oral thin film formulation can be a potential novel drug dosage form.

REFERENCES

1. Ishikawa T, Koizumi N, Mukai B. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PHM06) and spherical sugar granules. *Chem Pharm Bull* (Tokyo) 2001; 49: 230-32.
2. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Singledose pharmacokinetics of sublingual versus oral administration of micronized 17 betaestradiol. *Obstet Gynecol* 1997; 89: 34045.
3. R.P Walton Absorption of drugs through the oral mucosa. III Fatwater solubility coefficient of alkaloids. *Proc Soc Exp Bio Med* 1935; 32: 1488.
4. Kurosaki Y, Takatori T, Nishimura H, Nakayama T, Kimura T . Regional variation in oral mucosal drug absorption permeability and degree of keratinization in hamster oral cavity. *Pharm Res* 1991; 8: 1297-1301.
5. Ghosh TK, Chatterjee DJ, Pfister WR. Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceutical perspective. In: Ghosh TK and Pfister WR (Eds). *Drug Delivery to the Oral Cavity Molecules to Market*. NY, USA: CRC Press, 2005: 337-356.
6. Boer D et al. Drug absorption by sublingual and rectal routes. *British J Anaesthesia* 1984; 56: 69-82.
7. Mary Elizabeth RN, Martelli BS. *Sublingual and buccal medication administration*. Encyclopedia of Nursing and Allied Health, 20050229
8. Lea L. *Sublingual Administration*. Colon Health 1996; 13.
9. Malke, M., S. Shidhaye and V.J. Kadam, 2007. Formulation and evaluation of Oxacarbazine fast dissolve tablets. *Indian J. Pharmaceutical Sci*., 69(2): 211-214.