Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 5, Suppl 4, 2012 ISSN - 0974-2441

Research Article

MONTELUKAST SODIUM ORAL THIN FILMS: FORMULATION AND *INVITRO* EVALUATION

K.VIJAYA SRI[1]*, P.ROHINI[1] AND G. KAMALAKAR REDDY [2]

1.Malla Reddy College of Pharmacy (Affiliated to Osmania university) Maisamma Guda, Secunderabad -500014
2.**Formulation R&D, Hetero Labs Ltd., Secunderabad, Andhra Pradesh, India; Email:** vijayasree_2002@yahoo.co.in

Received: 9 September 2012, Revised and Accepted: 8 November 2012

ABSTRACT

Objective: Montelukast sodium is indicated for the prophylaxis and chronic treatment of asthma. Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules etc. The present investigation was undertaken with the objective of formulating of the montelukast sodium fast dissolving oral thin films allowing fast reproducible drug dissolution in oral cavity thus bypassing first pass metabolism, to enhance the convenience and compliance by the elderly and pediatric patients.
Materials and methods: Montelukast fast dissolving oral thin films were prepared by solvent casting method with using different film-forming agents like HPMC, PVP, PEG 400, glycerol as a plasticizer and mannitol as filler and sweetener. Oral thin films were evaluated for weight variation, thickness, surface pH, folding endurance, drug content, disintegration time, and *invitro* dissolution studies.
Results: Montelukast oral thin films based on evaluation studies HPMC showed optimum performance against other formulations. The prepared films were clear, transparent, and had a smooth surface.

Conclusion: It was concluded that the fast dissolving oral thin films of montelukast can be made by solvent casting technique with enhanced dissolution rate, better patient compliance and effective therapy.

Keywords: Montelukast sodium, solvent casting, mechanical properties, *invitro* dissolution and oral thin films.

INTRODUCTION

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing. The first developed fast-dissolving dosage form consisted of tablet form, and the rapid disintegrating properties were obtained through a special process or formulation modifications [(1)]. More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot-melt extrusion [(2)]. According to the film forming material characteristics, the manufacture of the dosage forms can present different critical issues. Common problems are caused by foaming during the film formation due to the heating of the material or solvent evaporation, the flaking during the slitting and the cracking in the cutting phase. Furthermore, the films should be stable to moisture overtime. Finally, to facilitate the handling they have to be flexible and exhibit a suitable tensile strength and do not stick to the packaging materials and fingers.

Formulation of these systems is usually straightforward; the polymer and drug are dissolved in a solvent and a film is cast by solvent evaporation [(3, 4)]. Most commercially available oral thin formulations, such as Oral film TM, (benzocaine) or Theraflu ®, (dextromethorphan / Phenylephrine HCl or Diphenhydramine HCl) are designed to deliver locally acting drugs or for mouth-freshening (such as Listerine Pocket Paks TM,).

Montelukast sodium is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies.[(5)] It is usually administered orally. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation. Montelukast sodium bioavailability is 63% . It has extensive first-pass metabolism and show a very poor dissolution rates in order to overcome this problem preparation of oral thin films.The main objectives of the present study were to prepare and evaluate the oral thin films of montelukast sodium and to study the various formulation variables that affect in vitro performance.

Materials And Methods

Materials

Montelukast sodium was received as a gift sample from Hetero Drugs, Hyderabad India. Two grades of HPMC (HPMC E 15 LV and

HPMC E 50 LV) were supplied from NP CHEM (Mumbai, India). Poly vinyl pyrrolidine (PVP), poly vinyl alcohol (PVA), methyl cellulose (MC) and PEG 400 was purchased from Sigma-Aldrich (Bangalore). Mannitol, glycerol (GLY) and citric acid were obtained by Carlo Erba Reagent. Menthol flavours were kindly gifted by Kerry Ingredients & Flavours (I). All solvents were of analytic grade.

Methods

Preparation of montelukast sodium oral thin films

The oral thin films of Montelukast sodium (MTS) were prepared in laboratory using HPMC by solvent casting method [(7)]. Hydroxy propyl methyl cellulose (HPMC) is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely Methocel E3 and Methocel E15 Premium LV were evaluated as primary film formers. For the fabrication of films, propylene glycol was used as a plasticizer, glycerin as humectant and mannitol was used as a sweetener. The required quantity of MTS was dissolved in 10 ml of distilled water containing various grades of HPMC to form polymeric dispersion. Briefly, propylene glycol, glycerin, aspartame and various polyhydric alcohols were dissolved in 5 ml of 50% v/v ethanol. Alcoholic solution and the polymeric dispersion were mixed to obtain a homogeneous dispersion and 20 ml of the dispersion was cast onto each polypropylene petriplate. The composition of various films is shown in Table 1. The dispersion was dried at 40–45 °C. The films were carefully removed from petri plates and stored in an air tight glass bottle. The films were evaluated for imperfections and cuts, peel ability without rupturing, folding and cracking endurance and surface roughness.

Evaluation of the montelukast sodium oral thin films

FT-IR Studies

Compatibility of drug and polymers was studied using Fourier Transform Infrared (FTIR) spectroscopy. FTIR Spectrum was recorded between 600-4000 cm^{-1} using Shimadzu 160a, Kyoto, Japan by KBr Disc method.

Mechanical Properties

Film thickness was evaluated using thickness tester (MitutoyoCo. Ltd., Japan, 0.001 mm capacity) at five locations and the mean thickness was calculated. Tensile strength was determined using

Universal Testing machine (Model AGS10kNG, Shimadzu, Japan) with load cell of 1kN. FDFs of size 7 x 1 cm^2 were placed between two clamps held 5 cm apart. The films were pulled by the clamp at a rate of 10 mm/min. Load vs. displacement data were recorded until the specimen broke. This data was then converted to stress vs. strain. Tensile strength and percentage elongation was calculated for each specimen by standard reported methods. [9] The folding endurance was measured manually by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. properties were measured in triplicate and reported as mean and standard deviation.

Table 1: different formulations of oral thin films of montelukast sodium

INGREDIENTS	MF1	MF2	MF3	MF4	MF5	MF6	MF7
MONTELUKAST SODIUM (mg)	10	10	10	10	10	10	10
HPMC E 15 LV (mg)	80	-	80	-	-	80	100
HPMC E 50 LV (mg)	-	50	-	-	-	-	-
PVA (2%W/V) (ml)	-	-	2.5	2.5	2.5	2.5	-
PVP (mg)	-	-	-	-	10	10	-
MC 360-400CPS (mg)	-	-	-	-	-	-	5
ETHANOL (ml)	1	1	1	1	1	1	1
GLYCEROL (ml)	0.02	0.02	0.02	0.02	0.02	0.02	0.02
PEG 400 (ml)	0.02	0.02	0.02	0.02	0.02	0.02	0.02
MANNITOL(5%W/V) (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MENTHOL (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
WATER UPTO ml)	5	5	5	5	5	5	5

The Percentage moisture absorption (PMA) test was carried out to check the physical stability of films at high humid conditions. In the present study the moisture absorption capacity of the MTS films were determined by keeping the preweighed films in desiccator at room temperature for 72 hours. Then they were taken out and exposed to 79.5% relative humidity (saturated solution of aluminum chloride). Average percentage moisture absorption of three films can be calculated by following equation

Percentage moisture absorption = (Final weight – Initial weight) X 100/Initial weight.

Percentage moisture loss(PML) was also carried to check the integrity of MTS films at dry condition. Three 2cm diameter films was cut and weighed accurately and kept in desiccators' containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture loss of three films was found out.

Percentage moisture loss = (Initial weight –Final weight) X 100/Final weight

Weight Variation

Weight variation is studied by individually weighing 10 randomly selected MTS films and calculating the average weight. The average weight should not deviate significantly from the average weight.

Surface pH

The surface pH of MTS fast dissolving oral thin films was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the film.

Table 2: evaluation for thickness, folding endurance, disintegration time, surface ph, % drug content, weight variation of montelukast sodium oral thin films formulation

FORMULATION	THICKNESS (MM)	FOLDING ENDURANCE	DISINTEGRATION TIME(SEC)	SURFACE pH	% DRUG CONTENT	WEIGHT VARIATION (MG)
MF1	0.22	297.33	10.30	6.87	99.46	43.44
	(0.01)	(2.51)	(1.52)	(0.02)	(0.15)	(0.57)
MF2	0.25	288.66	33.60	6.85	96.80	44.06
	(0.01)	(4.72)	(1.52)	(0.03)	(0.10)	(1.15)
MF3	0.23	297.66	25.30	6.91	98.16	43.50
	(0.01)	(2.08)	(1.52)	(0.02)	(0.25)	(1.00)
MF4	0.27	282.66	14.00	6.82	99.16	39.56
	(0.01)	(2.08)	(2.00)	(0.01)	(0.11)	(0.57)
MF5	0.24	284.33	18.00	6.89	98.33	38.63
	(0.02)	(3.05)	(1.52)	(0.20)	(0.15)	(1.52)
MF6	0.24	264.33	50.30	6.86	96.07	35.13
	(0.01)	(4.72)	(2.51)	(0.01)	(0.11)	(1.15)
MF7	0.27	297.00	57.60	6.93	97.27	41.03
	(0.01)	(2.00)	(2.51)	(0.01)	(0.10)	(1.52)

Drug content

Drug content of all batches of MTS thin films was determined by UV-spectrophotometric method. For this one strip of 4 cm^2 was dissolved in 100ml of pH 6.8 buffer. Then the solution was suitably diluted and the absorbance was recorded at 240nm.

Uniformity of drug content

The uniformity of dosage units of the oral film preparation was tested using 10 preparations, and the content of montelukast sodium was determined by UV-spectrophotometry. The acceptance value (AV) of the preparation is less than 15%, according to the JP15. While in USP27, the contents of preparations are between 85% and 115% and the relative standard deviation is less than or equal to 6.0%. AV for JP15 was calculated according to the following equation:

$$AV = |M - X| + ks$$

Where, M is label claim (100%), X the average (%) of individual contents, k the acceptability constant (2.2), and s is the standard deviation.

MONTELUKAST SODIUM ORAL THIN FILMS SOLID STATE EVALUATION

***In vitro* disintegration time**

A glass Petri dish (6.5 cm diameter) was filled with 10 ml of water and the film was carefully placed in the center. The set up was left undisturbed. The time for the film to completely disintegrate into fine particles was noted. The test was performed four times on each formulation and mean value was reported. Wherever applicable, the mean disintegration times were subjected to statistical analysis by non-paired student t test (Data Analysis tool, MS Excel 2000). Differences in means were considered statistically significant at $P<0.05$.

***In vitro* dissolution studies**

The dissolution rate of MTS films was studied in 900 ml of pH 6.8 buffer using USP dissolution test apparatus with basket stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. One film containing 25 mg of MTS oral thin film was used in each test. Samples of dissolution media (5 ml) were withdrawn at predetermined intervals suitably diluted and assayed for MTS at 240 nm respectively. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. The dissolution experiments were conducted in triplicate. Drug percent dissolved at 10 min (DP_{10}), values were calculated from the dissolution data given table 4.

Kinetic modeling of oral thin films

The dissolution profile of MTS oral thin films followed first order to ascertain the kinetic modeling of the drug release.

Zero order

In many of the modified release dosage forms, particularly sustained or controlled release dosage forms (those dosage forms that release the drug in planned, predictable and slower than the normal manner), is zero-order kinetic.

$m = k * t$

Where, k is zero-order constant, m is the % drug unreleased and t is the time. The plot of % drug unreleased (released) versus time is the linear.

First order

Most conventional dosage forms exhibits this dissolution mechanism. Some modified release preparation, particularly prolonged release formulations, adheres to this type of dissolution pattern.

$m = ea * e\text{-}bt$

Where, a is the intercept and b is the slop. It assumes that the drug molecules, diffuses out through a gel like layer formed around the drug during the dissolution process. A plot of log % drug release versus time is the linear.

Stability Studies

For stability testing the optimized formulation (SF7-HPMC E 15 LV+MC) were stored under controlled conditions of 40°C±2°C and 75%±5% RH over a period of 3 months according to the ICH guidelines. During storage the films were evaluated for their physical appearance, disintegration time, drug content and *invitro* dissolution studies.

RESULTS AND DISCUSSION

FTIR studies

The FTIR spectra of montelukast sodium and its physical mixtures are shown in figure 1. The FTIR spectrum of montelukast depicts a characteristic absorption band at 3437 cm^{-1} representing the presence of OH group. The CH_2 , C-N vibrations showed a characteristic absorption band in the region of 2926 cm^{-1} and 1265 cm^{-1}. The spectrum of montelukast- polymer physical mixtures showed absorption bands at 3414 cm^{-1}, 2926 cm^{-1} and 1266 cm^{-1} OH, The CH_2 and C-N. It indicates drug and drug containing physical mixture absorption bands were near that there was no chemical and physical change in the functional groups present in montelukast sodium.

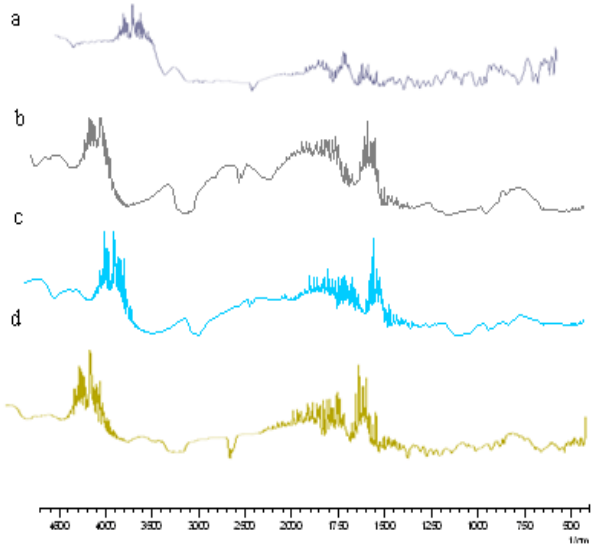

Figure 1: ft- ir spectra of a) montelukast sodium , b) hpmc e 50 lv, c) hpmc e 15 lv, d) physical mixture of polymers and montelukast sodium

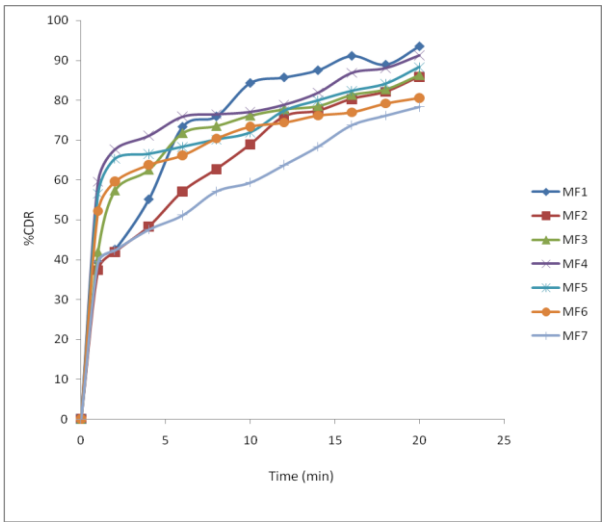

Figure 2: *invitro* dissolution profile for oral thin films of montelukast sodium

Mechanical Properties

As all the formulations contained different polymers, hence the thickness was varied in the range of 0.22mm to 0.27 mm. MF1 formulation have low thickness i.e. 0.22mm and formulation MF7 & MF4 have more thickness i.e 0.27mm. Percentage moisture absorption varied within in the range of 2.45 to 5.21%. Formulation MF4 showed high percentage moisture absorption i.e. 5.21% and formulation MF2 showed low percentage moisture absorption i.e 2.45%. It indicates that the films were stable. Percentage moisture loss was carried out to know the integrity of the film. Percentage moisture loss varied within the range of 1.44 to 3.70 %. MF3 showed less percentage moisture loss i.e. 1.44% and formulation MF4 showed more percentage moisture loss i.e. 3.7%. Swelling percentage varied within in the range of 26.3 to 59.66%. It was found to be more for formulation MF5 i.e. 59.6%. More swelling percentage indicates that the drug release is more and hence rapid onset of action. MF1 showed more percentage elongation i.e. 17.6 and MF5 formulations showed low percentage elongation i.e. 10.1 elongation indicates plasticity of the films.

The surface pH of the strips was ranging from 6.8 to 6.93. Since surface pH of films was found to be around neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity. MF7 had a pH of 6.93. Folding endurance is determined by folding the films of uniform cross section area and thickness until it breaks. It was measured manually and all the formulations showed good folding endurance. Formulation MF1batch has high folding endurance i.e. 297.33 and MF6 showed less folding endurance i.e. 264.33 compared to other formulations. As all the formulations showed folding endurance nearest to 300 it indicates good plasticity. Increase in number of folds was due to elasticity nature of polymer. Mechanical properties are mentioned in table no 2. weight variation, drug content, uniformity of drug content *and In vivo* disintegration time values are shown in table 3.

Table 3: evaluation for moisture absorption, moisture loss, degree of swelling and percentage elongation of oral thin films of montelukast sodium (n=3 mean±sd)

FORMULATIONS	MOISTURE ABSORPTION	MOISTURE LOSS	DEGREE OF SWELLING	% ELONGATION
MF1	3.50	1.50	34.00	17.63
	(0.020)	(0.100)	(0.250)	(0.152)
MF2	2.45	1.67	26.40	10.23
	(0.005)	(0.020)	(0.164)	(0.250)
MF3	2.74	1.44	26.39	10.30
	(0.011)	(0.015)	(0.020)	(0.300)
MF4	5.21	3.70	35.45	19.80
	(0.020)	(0.020)	(0.031)	(0.200)
MF5	4.42	2.12	59.66	10.10
	(0.005)	(0.068)	(0.011)	(0.100)
MF6	4.23	3.62	42.35	17.50
	(0.063)	(0.015)	(0.266)	(0.100)
MF7	2.64	1.69	37.64	15.00
	(0.005)	(0.015)	(0.021)	(0.200)

Weight variation

Weight variation was carried out and this varied within the range of 35.1 to 44.0 mg. As per USP requirements, the formulations were found to meet the criteria for weight variation.

Drug content

Drug content was evaluated and it varied within the range of 96.07±0.115 to 99.46. The drug content was found to be low for MF6 i.e. 96.07 and more for MF7 i.e. 99.46. As per USP requirements, drug content was found to be within the limits i.e. 85-115%.

Uniformity of drug content

Three film strips of 1cm^2 was cut from each film and estimated for drug content using UV-Spectrophotometric method. It was found that the drug was uniformly distributed throughout the film.

***In vivo* disintegration time**

In vivo Disintegrating time is defined as the time (seconds) at which a film breaks when brought into the contact with water or saliva. All the formulations were found to disintegrate within 60 sec. Formulation MF1 showed less disintegration time i.e. 10.3sec and formulation MF7 showed more disintegration time i.e. 57.6sec.

***In vitro* dissolution studies**

In vitro drug release was carried out in USP basket type dissolution apparatus using 0.5% SLS. MF1 formulation released more amount of drug i.e. 93.49 and formulation MF7 released less amount of drug i.e. 78.31%. Dissolution rate increases with decrease in disintegration time. *In vitro* dissolution studies graphs are mentioned in fig 3. More amount of drug release indicates rapid onset of action and hence faster relief.

Kinetic modeling of oral thin film

Table 4 and fig 3 showing R_2 values for zero order release and first order release. The values for first order were closer to 1 than those for zero order. So, it was assumed that all the formulations followed first order kinetics. The release is found concentration dependent.

Stability studies

When the oral film preparation was stored either in the aluminum package or under unwrapped condition at 40 ◦C and 75% in humidity for 4–8 weeks, no apparent changes in the shape, color or flexibility were observed.

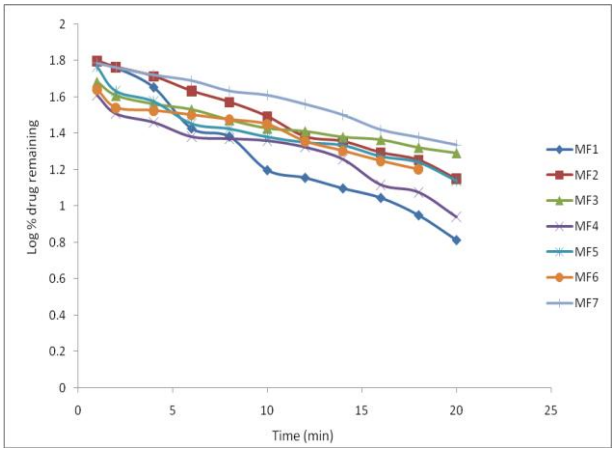

Fig 3: FIRST ORDER KINETICS GRAPH OF MONTELUKAST SODIUM ORAL THIN FILMS

Table 4: dissolution parameters and kinetic modeling of montelukast sodium oral thin films

FORMULATIONS	$K^{-1}(MIN^{-1})$	T_{50}	R	DP_{10}	FIRST ORDER R^2	ZERO ORDER R^2
MF1	0.11	6.01	0.985	68.92	0.972	0.839
MF2	0.07	9.11	0.996	68.92	0.993	0.809
MF3	0.04	15.8	0.978	76.11	0.957	0.617
MF4	0.06	10.3	0.969	77.11	0.940	0.516
MF5	0.062	11.1	0.965	71.97	0.932	0.547
MF6	0.057	12.0	0.976	73.31	0.954	0.526
MF7	0.052	13.0	0.994	59.33	0.989	0.778

CONCLUSION

Fast dissolving films fulfill all the aforementioned requirements of potential solid oral dosage form for local delivery of montelukast sodium. Fast dissolving film when placed in the oral cavity quickly gets hydrated, sticks onto the site of application and then disintegrates to release the drug [9]. Thus, a fast dissolving film is a unique solid oral dosage form and has valuable advantages [10]. In conclusion, we reported here the formulation of montelukast sodium -containing oral disintegrating film. The film preparation met the criteria of AV in the dosage uniformity test for JP15 and USP27, moreover, it revealed an excellent stability and dissolution profile.

ACKNOWLEDGEMENT

The authors are thankful to M.Sudhakar principal of Malla Reddy college of Pharmacy, Hyderabad for providing the facility to carry out the research work. The authors are thankful to Hetero Lab Ltd, Hyderabad, for providing the gift sample of montelukast sodium.

REFERENCES

1. Sandri G., Bonferoni MC., Ferrari F., Rossi S., Caramella C. Differentiating factors between oral fast-dissolving technologies, Am. J. Drug Deliv .2006; 4;249–262.
2. Borsadia SB, O'Halloran D, Osborne JL. Quick-dissolving films: A novel approach to drug delivery. Drug Deliv Techno.l 2003; 3:1.
3. Ahmed MG, Narayana CR, Harish NM, Prabhakar P. Formulation and In-vitro evaluation of Chitosan films containing tetracycline for the treatment of periodontitis. Asian J Pharm 2009; 3;113- 9.
4. Hiroyoshi Shimoda , Kazumi Taniguchi, Misao Nishimura , Katsuhiko Matsuura , Tadao Tsukioka Hirotaka Yamashita, Naoki Inagaki , Kazuyuki Hirano, Mayumi Yamamoto Yasutomi Kinosada ,Yoshinori Itoh Preparation of a fast dissolving oral thin film containing dexamethasone:A possible application to antiemesis during cancer chemotherapy Eur J Pharm and Biopharmaceutics 2009 ; 73; 361–365.
5. Rang HP, Dale MM., Ritter JM., Moore PK. Pharmacology. In Rang HP, 5th ed. Churchill Livingstone Publishing co. 2003; 236&347.
6. Fulzele SV., Sattuwar PM., Dorle AK. Polymerized rosin: novel film forming polymer for drug delivery. Int. J. Pharm. 2002; 249; 175-184.
7. Satishbabu BK, Srinivasan BP. Preparation and evaluation of buccoadhesive films of atenolol. Indian J Pharm Sci 2008; 70;175-9.
8. Mona SA, Semalty KG. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian J Pharm Sci 2008; 70;43-8.
9. Borsadia SB., O'Halloran D., Osborne JL. Quick dissolving films-a novel approach to drug delivery. Drug Deliv Tech 2003; 2.
10. Liang AC., Chen L. Fast dissolving intraoral drug delivery systems. Expert Opin. Ther. Pat 2001; 11; 981–986.