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Formulation and Evaluation of Montelukast Sodium Fast Dissolving Tablet

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ABSTRACT

The objective of the study is to develop Montelukast Sodium Fast Dissolving tablets. ***Montelukast*** *is a leukotriene receptor antagonist used as part of an asthma therapy regimen, to prevent exercise induced bronchoconstriction (EIB), and to treat seasonal allergic rhinitis. Fast dissolving tablets can be prepared by direct compression of the drug and suitable concentration of super-disintegrants along with other excipients. Fast dissolving tablets were prepared by direct compression method. The evaluation data for post-compression parameters such as weight variation, hardness, thickness, friability, drug content, uniformity of drug content and in-vitro dissolution indicated that the prepared tablets were well within the specified standards. The formulation F9 is considered as best formulation as the ratio of natural and synthetic polymer is equal and showed 91.03% drug release, which revealed that the drug release rate of the immediate release tablets is concentration independent. Various approaches have been used to calculate drug release kinetics.*

Keywords: *Montelukast Sodium, Direct Compression, super-disintegrants, sodium starch glycolate, direct compression, etc.*

INTRODUCTION

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and an economical method of drug delivery having the highest patient compliance[1]. Tablet is most popular among all dosage forms existing today because of convenience of self-administration, compactness and easy manufacturing [2]. Many patients express difficulty in swallowing tablets and hard gelatin capsules, resulting in non-compliance and ineffective therapy [3]. To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets [4]. United States Food and Drug Administration (FDA) defined fast dissolving tablet (FDT) as “a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed up on the tongue” [5]. Their characteristic advantages such as administration without water, patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market [6].

Montelukast sodium is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It is usually administered orally. Montelukast sodium is freely soluble in ethanol, methanol and water and practically insoluble in acetonitrile and its bioavailability is 63% [7,8].

In the present study an attempt has been made to prepare fast dissolving tablets of Montelukast sodium in the oral cavity with enhanced dissolution rate and hence improved patient compliance. The basic approach used in the development of Montelukast sodium fast dissolving tablets by using co-processed super-disintegrants containing crospovidone and sodium starch glycolate was studied. The concept of formulating fast dissolving tablets (FDT) of Montelukast sodium using co-processed super-disintegrants helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost-effective direct compression technique. These systems may offer superior profile with potential mucosal absorption, thus increase the drug bioavailability.
These systems are interchangeably called mouth dissolving tablets, melt-in-mouth tablets, porous tablets, oro-dispersible, quick dissolving or rapidly disintegrating tablets.

IDEAL PROPERTIES OF FAST DISSOLVING TABLETS

1) The tablets should disintegrate or dissolve in the mouth (in saliva) within few seconds.
2) Should not require water or any liquids to swallow or to show its action.
3) Should allow high drug loading.
4) Should be compatible with taste masking and other excipients.
5) Should have pleasing mouth feel.
6) Should not leave any residue in the mouth after administration.
7) Should have low sensitivity to environmental conditions (temperature, humidity, etc.)
8) Should be adoptable to existing processing and packaging machinery.
9) Excipients should have high wettability.
10) Should have rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus, producing rapid onset of action.
11) Should allow packaging equipments at low cost.
12) Should have sufficient strength to withstand rigors of the manufacturing process and post manufacturing handling.
13) Be harder and less friable.[9]

SALIENT FEATURES OF FDT

1) Does not require water for oral administration
2) Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling
3) Allow high drug loading
4) Insensitive to environmental conditions such as humidity and temperature
5) Adaptable and amenable to existing processing and packaging machineries
6) Cost effective.
7) Have a pleasant mouth feel. [10]

MERITS OF FAST DISSOLVING TABLETS

1) Improved compliance/added convenience
2) No water needed
3) No chewing needed
4) Better taste
5) Improved stability
6) Suitable for controlled as well as fast release actives
7) Allows high drug loading
8) Ability to provide advantages of liquid medication in the form of solid preparation
9) Adaptable and amenable to existing processing and packaging machinery
10) Cost- effective.[10]

DEMERITS OF FAST DISSOLVING TABLETS

1) Drugs with relatively large doses are difficult to formulate into FDTs.
2) Patients who concurrently take anti-cholinergics may not be the best candidates for FDTs.
3) Tablets usually have insufficient mechanical strength. Hence, it requires careful packaging and handling
4) Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
5) They are more susceptible to degradation by humidity and temperature.
6) Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
7) Some time it possesses mouth feeling.
8) MDT requires special packaging for properly stabilization & safety of stable product.
9) Drugs difficult to formulate into FDT with relatively larger doses.
10) Drugs with short half-life and frequent dosing and those whom require controlled or
11) Sustained release is unsuitable candidates of FDT. [11]

CHALLENGES IN FORMULATION OF FAST DISSOLVING TABLETS (FDTS)

1) **Mechanical Strength and Disintegration Time:** It is obvious that increasing the mechanical strength will delay the disintegration time. So, a good compromise between these two parameters is always essential. FDTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge.
2) **Taste Masking:** As most drugs are unpalatable, rapid disintegrating drug delivery systems usually contain the medicament in a taste masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.
3) **Aqueous Solubility:** Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol that can induce crystallinity and hence, impart rigidity to the amorphous composite.
4) **Hygroscopicity:** Hygroscopicity is, of course, an important characteristic of a powder. It can be shown, roughly, for a fairly soluble compound that the hygroscopicity is related to its solubility. FDTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast-dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect FDTs from various environmental conditions.
5) **Amount of Drug:**The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 4 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.
6) **Size of table:** It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.
7) **Mouth feel:** FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible.

Moreover, addition of flavors and cooling agents like menthol improve the mouth feel.

8) **Sensitivity to environmental conditions:** FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature asmost of the materials used in FDTs are meant to dissolve in minimum quantity of water. [11]

Montelukast sodium is an anti-asthmatic; it mainly prevents leukotriene mediated effect associated with asthma and allergic arthritis. Mouth dissolving tablets of montelukast sodium was prepared by direct compression method using super-disintegrants such as croscarmellose sodium and crospovidone. The compatibility of the drug in the formulations was confirmed by IR studies. The formulations were subjected to precompression and postcompression parameters and the results were found to be within acceptable limits. The formulated tablets disintegrated in less than 26.33 sec fulfilling the official requirements for dispersible tablets. The rapid drug dissolution was observed in the formulations containing croscarmellose sodium and followed first order release kinetics. Finally, it can be concluded that mouth dissolving tablets of montelukast sodium can be prepared by direct compression method using croscarmellose sodium as superdisintegrant. [12]

METHODS

Drug Related Studies

Identification of pure drug by IR Spectroscopy

The FTIR spectrum of the sample of the drug was compared with the standard FTIR spectra of the pure drug.

Determination of melting point

Melting point of Montelukast Sodium was determined by open capillary method.

Solubility Analysis

Solubility analysis is carried out for Montelukast Sodium samples in various solvents. 10 mg pure drug was dissolved in 10ml of different solvents i.e. water, ethanol and dimethyl formamide solubility was determined. [13]

Determination of Absoption Maxima (λmax)

Standard stock solution of **r**Montelukast Sodium was prepared in 0.5% SLS working standard solution of Montelukast Sodium was prepared by taking suitable aliquots of standard drug solution (1000µg/ml) and volume was made up to 10ml with 0.5% SLS. The resulting solutions were then scanned in the UV range (200-400) using UV double beam spectrophotometer using blank. The spectrum of absorbance versus wavelength was recorded and analyzed for the absorbance maximum (λmax). [14]

Preparation of Standard calibration curve for Montelukast Sodium

Accurately weighed 100mg of Montelukast Sodium was dissolved with 0.5% SLS in 100ml volumetric flask. From this stock-I, 10ml was pipette in 100ml volumetric flask and volume was made with 0.5% SLS to make second solution. From the second stock solution different aliquots were prepare solution in the range 5-30µg/ml. The standard curve was obtained by plotting absorbance versus concentration. [14,15]

Method of preparation of fast dissolving tablets

Fast dissolving tablets each containing Montelukast Sodium equivalent to 10 mg of

Montelukast, were prepared using super-disintegrants, sodium starch glycolate, crospovidone and guar gum according to the formulae given in Table 4. The average weight of the tablets was 180 mg. The ingredients were dispensed in required quantities and sieved through #60 mesh, except magnesium stearate. After mixing the drug and the excipients for 20 min, magnesium stearate was added and further mixed for additional 2 min. The tablet mixture was then compressed (8 mm diameter, convex punches) using double rotary tablet compression machine. [16]

Table-Formulation composition of Montelukast Sodium fast dissolving tablets

Name of Ingredients	Quantity (mg/ tablet)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Montelukast Sodium	10	10	10	10	10	10	10	10	10	10
Crospovidone	20	30	30	-	-	-	20	30	20	30
SSG	-	-	-	20	30	40	-	-	-	-
Guar gum	-	-	-	-	-	-	20	10	-	-
Stevia powder	9	9	9	9	9	9	9	9	9	9
Mannitol	15	15	25	15	15	15	15	15	35	25
Mg stearate	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
MCC pH 101	122.4	112.4	102.41	122.4	112.4	102.4	102.4	102.4	102.4	102.4
Total	180	180	180	180	180	180	180	180	180	180

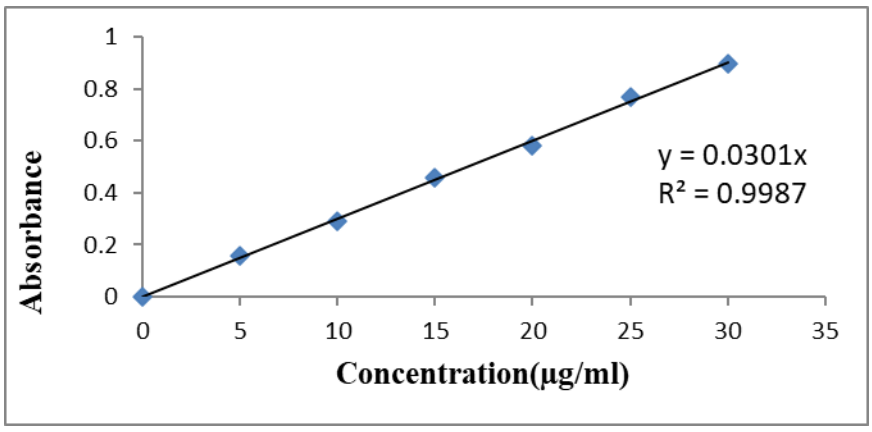
RESULT AND DISCUSSION

Drug Identification Tests

Melting point Determination: Melting point of Montelukast Sodium was determined by capillary method and results fount to be 108-110°C, which complied with the standard monograph, indicating the purity of the drug.

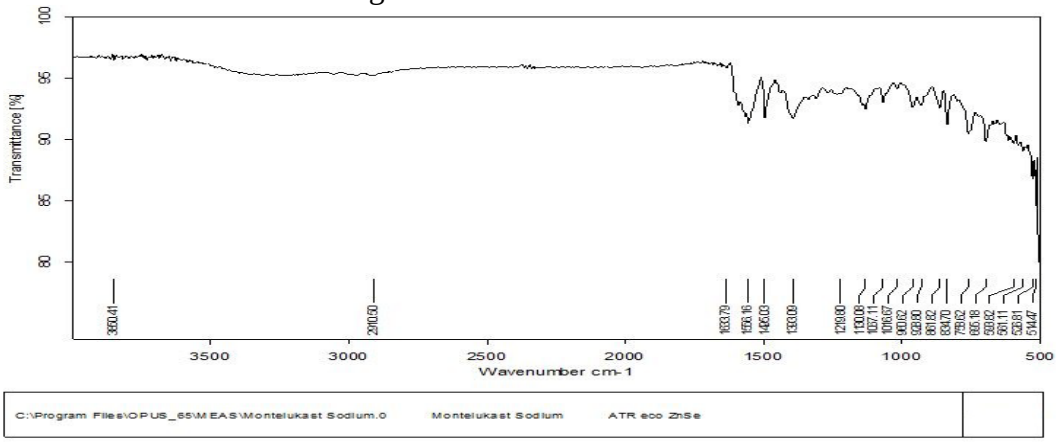
Solubility analysis: Montelukast Sodium found to be soluble in water, ethanol and dimethyl formamide

Calibration curve of Montelukast Sodium: Montelukast Sodium obey the Beer's law in concentration range of 5-30 µg/ml in 0.5% SLS with regression coefficients (R^2) of 0.9987. The calibration data is given table and calibration curve wasconstructed in graph below.

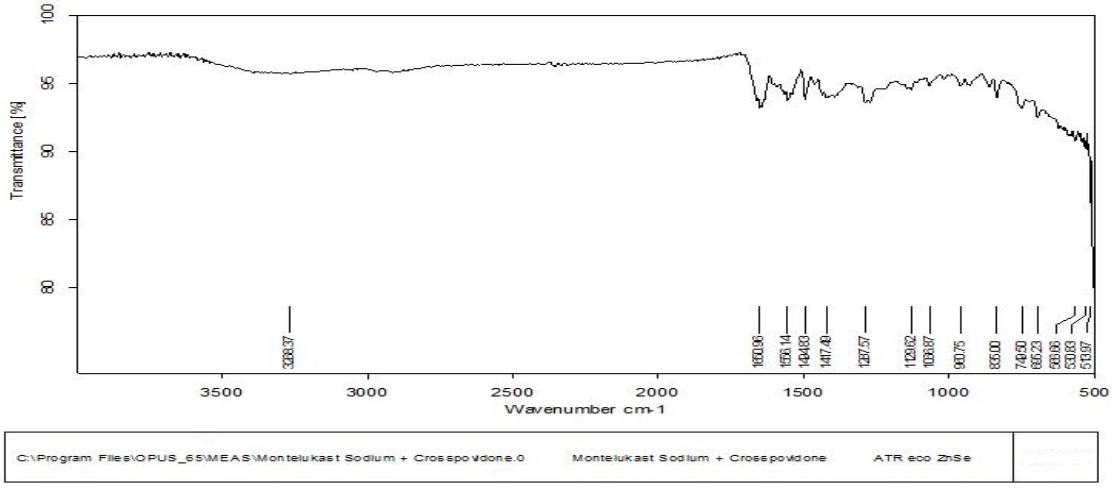


FTIR Spectrophotometry

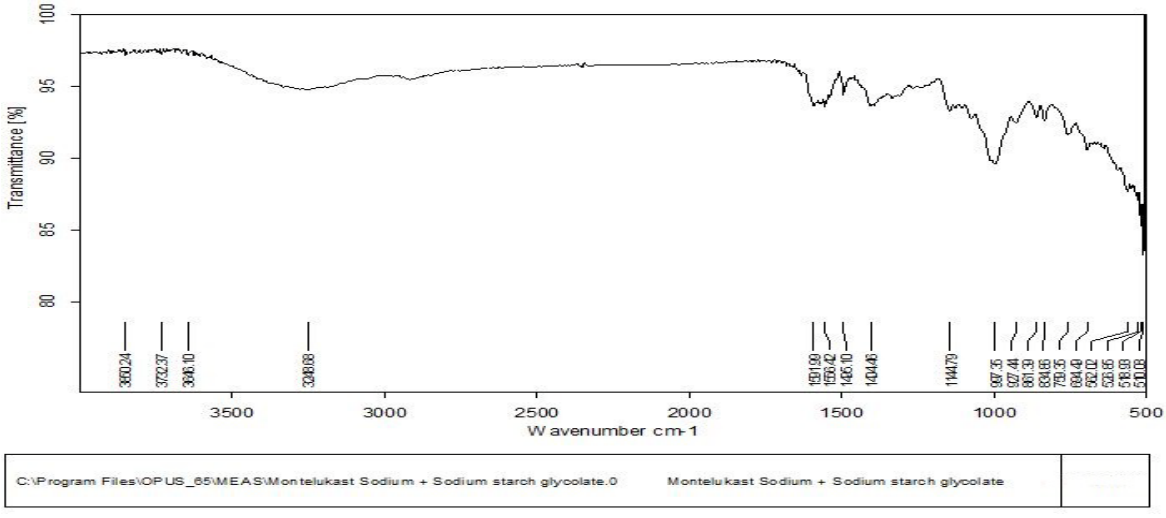
Compatibility study of drug and ingredients was performed by FT-IR technique. Drug and polymers are used to prepare oral dispersible tablet were checked for compatibility study by carrying out FTIR spectroscopy. The FTIR spectra obtained for pure drug and drug-polymers mixture from 4000 to 400 cm^{-1} are given as follows.



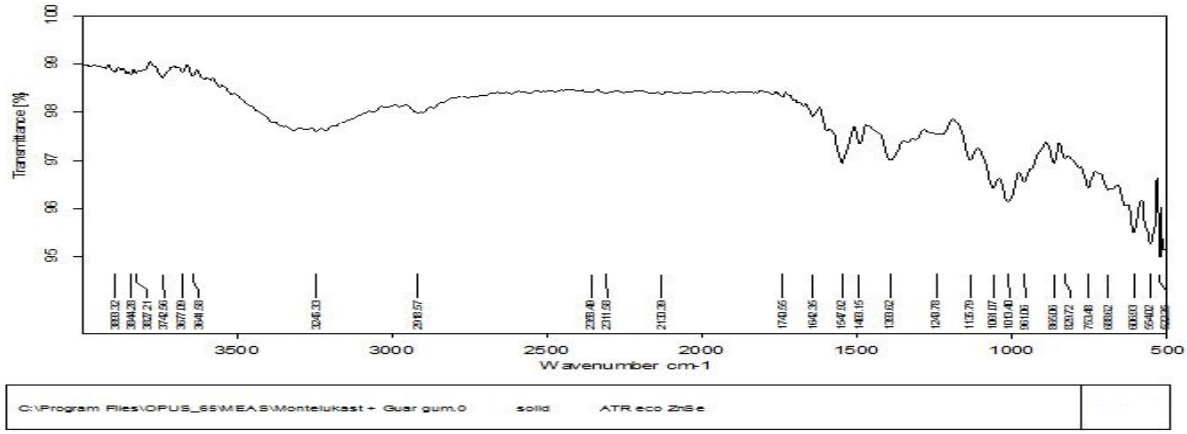
FTIR spectra of Montelukast Sodium



FTIR spectra of Montelukast Sodium+ Crospovidone



FTIR spectra of Montelukast Sodium + Sodium Starch Glycolate



FTIR spectra of Montelukast Sodium +Guar Gum

EVALUATION OF TABLETS OF ALL FORMULATIONS

Pre-compression parameters of Montelukast Sodium powder mixture

Formulation Batch	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio	Angle of repose (°)
F1	0.315±0.003	0.358±0.004	12.01±0.76	1.13±0.008	27.30±1.13
F2	0.303±0.001	0.342±0.006	11.40±0.14	1.12±0.003	28.20±1.08
F3	0.312±0.006	0.363±0.002	14.04±0.04	1.16±0.012	29.80±1.19
F4	0.310±0.03	0.359±0.003	13.64±0.06	1.15±0.007	27.90±1.08
F5	0.319±0.012	0.367±0.004	13.07±0.15	1.15±0.004	28.50±0.98
F6	0.315±0.014	0.361±0.003	12.74±0.21	1.14±0.016	28.90±1.16

Post-compression evaluations of Montelukast Sodium tablet

Formulation Batch	Wt. variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%) n=10	Drug Content (%)	Disintegration time (Seconds)
F1	179.4±0.07	3.0±0.20	3.0±0.03	0.33±0.02	98.0±1.02	21±0.04
F2	180.0±1.20	3.0±0.30	3.0±0.02	0.35±0.03	95.0±1.03	14±0.08
F3	179.6±0.30	3.5±0.20	3.4±0.11	0.31±0.02	97.0±1.05	09±0.20
F4	179.2±0.09	3.5±0.18	3.4±0.20	0.31±0.16	97.0±1.05	30±0.05
F5	180.5±0.06	3.5±0.12	3.4±0.08	0.32±0.12	98.0±1.10	36±0.05
F6	181.5±0.08	3.5±0.20	3.4±0.15	0.33±0.11	100±1.02	31±0.10
F7	179.3±2.00	3.6±0.17	3.2±0.30	0.34±0.17	96.0±1.04	18±1.02
F8	181.0±1.20	3.6±0.40	3.2±0.60	0.35±1.02	95.0±0.06	17±1.04
F9	179.8±1.00	3.6±0.13	3.2±1.08	0.35±0.09	91.0±0.08	22±0.20
F10	181.1±0.60	3.2±1.20	3.8±0.70	0.34±0.10	93.6±1.04	18±1.06

Note: All values are expressed as mean ± SD. n=3.

PRE-COMPRESSIONAL EVALUATION PARAMETERS

Results of the pre-compressional parameters performed on the powder blend for tablets formulations F1 to F10. The angle of repose for all the formulations was found to be within the range of 27.30 ± 1.13 to 29.90 ± 1.23, showing good flow characteristics. Hausner's ratio was found to be in the range of 1.12 ± 0.003 to 1.17 ± 0.006 and compressibility index was found to be in the range of 11.40 ± 0.14to 14.97 ± 0.18, indicating good flow ability of the tablet formulations.

POST-COMPRESSION PARAMETERS

- **Shape and appearance:** White round flat uncoated tablets having break line on one side.
- **Weight Variation:** Prepared tablets of all formulations were evaluated for weight variation and standard deviations from the average weight. The average weights of all the

formulations were within the range of 179.2±0.09 to 181.5±0.08. All the tablets passed the weight variation test, i.e., the average percentage weight variation was found to be within the prescribed pharmacopoeia limits of ±7.5%.

- **Tablet Thickness and Hardness:** The thickness of the tablets from batch F1 to F10 was found to be between 3.0 ± 0.03 to 3.8 ± 0.70 mm and hardness was found to be within the range of 3.0 ± 0.20 to 3.6 ± 0.50 Kg/cm^2. The low standard deviation values indicate that the thicknesses as well as hardness of all the formulations were almost uniform and also the tablets possess good mechanical strength with sufficient hardness.
- **Friability:** The friability of the formulations (F1 to F10) was found to be between 0.31±0.02% to 0.35±1.02%.The obtained results were found to be within the range (<1%) in all the formulations indicating tablets possess good mechanical strength.
- **Drug Content Uniformity:** The Percentage of drug content for F1 to F10 was found to be in the range of 91.0 ± 0.05% to 106.0 ± 0.09 %.The results were within the limit (NLT 90% and NMT 110%) as specified in Indian pharmacopeia.
- **Disintegration Time:** The *in-vitro* disintegration time was found to be very less for F3 formulation that is 09 ± 0.20 seconds. As the concentration of super disintegrants increases, there is decrease in the disintegration time.
- ***In-Vitro* Dissolution Studies:** The cumulative percentage drug released from each tablet formulation wasstudied at different time intervals.The dissolution profile for formulation F1 to F10.Formulation F9 shown better dissolution profile when compared to remaining formulations.

Table - % drug release of Montelukast Sodium fast Dissolving tablets (F1-F10)

S.No.	Time in Mins	% Cumulative Drug Release									
		Formulation Code									
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	0.5	5.40	31.5	36.5	39.5	39.0	39.75	37.75	45.25	46.25	40.25
2	1	6.00	59.42	59.45	56.96	51.96	49.47	51.95	54.50	56.50	53.47
3	1.5	6.57	65.0	68.28	68.28	63.25	60.74	57.99	70.80	73.31	67.76
4	2	7.07	68.11	73.15	71.91	70.60	68.07	65.56	75.94	80.72	73.64
5	3	7.53	70.23	75.30	76.05	73.24	72.70	70.92	79.60	83.66	75.54
6	4	9.67	72.36	76.97	77.04	75.39	75.35	72.31	82.54	85.12	78.45
7	6	10.90	73.26	78.13	78.39	78.05	77.00	74.95	84.74	87.08	80.38
8	8	12.00	73.90	79.06	78.56	79.97	78.42	76.61	86.95	89.05	82.32
9	10	13.30	74.80	80.23	78.73	81.90	79.59	77.77	88.16	91.03	84.01

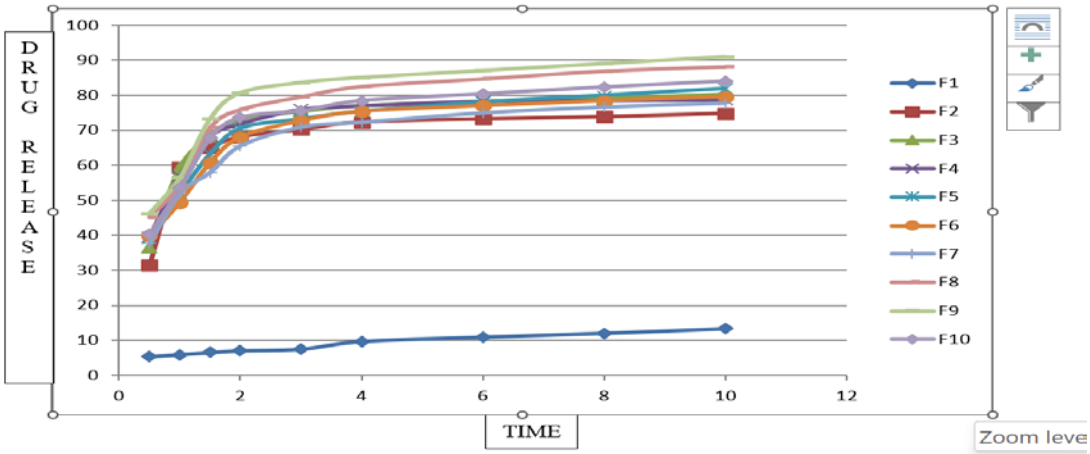


Fig - In-vitro drug release profiles of Montelukast sodium fast dissolving tablets (F1 to F10)

- **Drug Release Kinetics:** The mechanism of drug release from formulation F9 were characterized by zero order kinetics, first order kinetics, Higuchi's kinetics, Korsmeyer-Peppas model plots as ore shown graph 10. It was observed that the high correlation coefficient (R2) was found to be 1. first order kinetics, which indicates the drug release rate of fast dissolving tablets would be dependent of its concentration.
- **Stability Studies:** From the stability studies, it was clear that the formulation was physically and chemically stable for 90 days. And there was no significant change in the physical parameters, drug content and *in-vito* dissolution release profiles.

Table - Release Kinetic Models of the Formulations (F1-F10)

Code	Zero order	First order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F1	0.9338	0.9352	0.9075	0.8709
F2	0.8729	0.7668	0.8058	0.7825
F3	0.6342	0.5017	0.548	0.5193
F4	1	1	1	1
F5	0.9786	0.9636	0.9665	0.9359
F6	0.9524	0.9798	0.9685	0.9627
F7	0.9772	0.856	0.9943	0.9996
F8	1	1	1	1
F9	1	1	1	1
F10	0.9661	0.8537	0.9247	0.8982

CONCLUSION

Fast dissolving tablets of Montelukast Sodium were successfully prepared to treat the asthmatic condition. According to all these evaluation parameters, formulation (F9) showed better drug release. Formulation F9 showed 91.03 % release of the drug in 10 min. Formulation was found stable at temp 40 ± 2^0C and 75±5% RH.

REFERENCES

1) Rajkumar Goyal, Satyendra Singh Baghel, Ashish Pathak, Kshamashil Sharma, Gourav Tiwari and Rituraj Shivhare. A Review on Formulation & Evaluation of Orodispersible Tablets (Fast Dissolving Tablet). WJPR. 2012; 1(3): 576-90.
2) N. Kanakadurgadevi, A. Prameela Rani, B. Sai Mrudula Formulation and evaluation of oral disintegrating tablets of Montelukast sodium: effect of functionality of superdisintegrants. JPR. 2010; 3(4): 803-08.
3) S. Dineshmohan, K. Vanitha, A. Ramesh, G. Srikanth and S. Akila. Formulation and Evaluation of Salbutamol Sulphate Fast Dissolving Tablet. IJRPBS. 2010; 1(2): 105-108.
4) Jeevanadham S, Dhachinamoorthy D, Chandra Shekar KB, Muthukumaran M, Sriram N, Joyasaruby J. Formulation and evaluation of naproxen sodium orodispersible tablets-A sublimation technique. AJP. 2010; 4 (1): 48-51.
5) Praveen Khirwadkar, Kamlesh Dashora. A Review: Fast Dissolving Drug Delivery System: Current Developments In Novel System Design and Technology. IJBAR. 2012; 03(02): 82-98.
6) Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation Design and Optimization of Mouth Dissolve Tablets of Nimesulide Using Vacuum Drying Technique. AAPS PharmSciTech. 2004; 5(3): 36.

7) Vijaykumar Ghorwade, Ajay Kumar Patil, Satish Kumar Patil, Karunasri Srikonda, Raghavender Kotagiri and Priya Patel. Development and Evaluation of Fast-Dissolving Film of Montelukast Sodium. WJMPBS. 2011; 1(1): 06-12.
8) Dr. Raghavendra Rao N. G and Upendra Kulkarni. Formulation and Design of Fast Dissolving Tablets of Felodipine Using Novel Co-Processed Superdisintegrants. IJPRD. 2010; 2(9): 113-121.
9) Gupta AK, Mittal A, Jha KK. Fast Dissolving Tablets. *Pharma Innovation*. 2012; 1(1): 1-8.
10) Siddiqui MN, Garg G, Sharma PK. Fast Dissolving Tablets: Preparation, Characterization and Evaluation. *Int J Pharm Sci Rev Res*. 2010; 4(2): 87-6.
11) Nautiyal U, Singh S, Singh R, Kakar S. Fast Dissolving Tablets as A Novel Boon. *J PharmaChem Bio Sci*. 2014; 2(1): 5-26.
12) Patil AK, Aman T, Bharghava BN, Abhilash P, Turaga M, Kulkarni S. Formulation and Evaluation of Mouth Dissolving Tablet of Montelukast Sodium. *Res Jpharma Bio chem Sci.* 2011; 2(3): 268-74.
13) Cayman chemical, Product information; item number: 10008318; Montelukast sodium.
14) Kuldeep S, Paramdeep B, Pragati S. Validated UV Spectroscopic method for estimation of Montelukast Sodium. *Int J PharmaSci and Res.* 2017: 6(11); 4728-32.
15) RM Singh, PK Saini, SC Mathur. Development and validation of a RP-HPMC method for estimation of Montelukast Sodium in bulk and in tablet dosage form. *Sci Pub Ind Pharm Association.* 2010; 72(2): 235-37.
16) Errolla M, Kumar GBK, Ahmed MG, Kumar KP. Formulation and Evaluation of Montelukast Sodium Fast Dissolving Tablets. *Asian J Bio Pharma Sci*. 2012; 2(14): 75-2.