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RESEARCH ARTICLE

Formulation and Evaluation of Montelukast Sodium Fast Dissolving Tablets

Errolla Mahesh, G.B. Kiran Kumar, Mohammed G Ahmed, Kiran kumar. P

Department of Pharmaceutics, SAC College of Pharmacy, B.G.Nagara-571448

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ABSTRACT

In the present work fast dissolving tablets of Montelukast sodium were prepared using novel co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate in the different ratios (1:1, 1:2 & 1:3) in vice versa. Montelukast sodium is a drug of choice in treatment of asthma and allergic rhinitis. Drug compatibility with excipients was checked by FTIR studies. After examining the flow properties of the powder blends the results were found to be within prescribed limits and indicated good flowing property and it was subjected to tablet compression. All the formulations were subjected to post compression parameters like hardness and friability (≤1%), indicated that tablets had a good mechanical strength and resistance. Drug content was found to be in the range of 93.51 to 98.79 %. The wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 20 to 55 sec. Among all the designed formulations, formulation F9 was found to be promising and showed an *in-vitro* disintegration time of 25 sec, which facilitates faster disintegration in the mouth. When compared to marketed product, the formulation F9 containing co-processed superdisintegrant (1:3 mixture of sodium starch glycolate and crospovidone) emerged as the overall best formulation based on drug release characteristics with 0.5% SLS in distilled water as dissolution medium. Short-term stability studies on promising formulation F9 indicated that there were no significant changes in hardness, drug content and *in-vitro* drug release. From this study, it can be concluded that dissolution rate of Montelukast sodium FDTs could be enhanced by tablets containing co-processed superdisintegrant.

Keywords: Co-processed superdisintegrants, Montelukast sodium, crospovidone, sodium starch glycolate and direct compression.

1. 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 noncompliance 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

*Corresponding author: Errolla Mahesh, | Department of Pharmaceutics, SAC College of Pharmacy, B.G.Nagara-571448.|
Email: maheshpharma888@gmail.com

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 had 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 superdisintegrants containing crospovidone and sodium starch glycolate was studied. The concept of formulating fast dissolving tablets (FDT) of Montelukast sodium using co-processed superdisintegrants 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 also called mouth dissolving tablets, melt-in-mouth tablets, Reprimelts, porous tablets, Oro dispersible, quick dissolving or rapidly disintegrating tablets.

2. MATERIAL AND METHODS:

Montelukast sodium as procured as a gift sample from Dr. Reddy's Laboratories Limited, Hyderabad, India. Superdisintegrants like Crospovidone and Sodium starch glycolate. Other excipients like Mannitol, Microcrystalline cellulose, Sodium saccharin, flavor, Sodium lauryl sulphate (SLS), Talc, and Magnesium stearate purchased from S.D. fine chem., Mumbai.

2.1. Preparation of Co-processed Superdisintegrants:

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and sodium starch glycolate (in the ratio of 1:1, 1:2 and 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60 ºC for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use.

2.2. Preparation of fast dissolving tablets by direct compression method

Montelukast sodium fast dissolving tablets were prepared by direct compression method by using co-processed superdisintegrants like Crospovidone, Sodium Starch Glycolate. Mannitol, Microcrystalline Cellulose as a diluent, Sodium saccharin as a sweetening agent, Mint as a flavor, Magnesium Stearate, Talc used as a lubricant and glident. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of drug as well as other components and compressed into tablets of 150mg using 8mm round flat punches on 12-station rotary tablet machine.

2.3. Evaluation of physical properties

Evaluation of blended characteristics of Montelukast sodium

Determination of angle of repose[9, 10]

Angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane:

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ = the angle of repose, h = height of the heap of the powder, r = radius of the heap of the powder

Determination of Bulk Density and Tapped Density[9]

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the Initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulae.

$$\text{Bulk density} = W / V_O$$

$$\text{Tapped density} = W / V_F$$

Where, W = weight of the granules, V_O = initial volume of the granules, V_F = final volume of the granules.

Hausner's Ratio:[9]

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \text{Tapped density/Bulk density}$$

Compressibility index (Carr's Index):[10, 11]

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$CI = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

2.4. Evaluation of Montelukast sodium fast dissolving tablets

Weight variation[9]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

Tablet hardness[9]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability[9]

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Tablet thickness[9]

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

Content Uniformity[9]

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg was weighed accurately and dissolved in 100ml of 0.5% of Sodium Lauryl Sulphate (SLS) in water. The solution was shaken thoroughly. The un dissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 345.5 nm. The concentration of the drug was computed from the standard curve of the Montelukast sodium in 0.5% of SLS in water.

Disintegration time[9]

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electro lab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing 0.5% of SLS in water at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Wetting time[2]

10 ml of distilled water containing Eosin, a water-soluble dye was placed in a petri dish of 10 cm diameter. Tablets were carefully placed in the centre of the petri dish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results are presented as mean value of three determinations.

Water absorption ratio[2]

A piece of tissue paper folded twice was placed in a

small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio indicated by R, which is calculated by using the below mentioned equation.

***In-vitro* dissolution studies[2]**

Dissolution testing of Montelukast sodium fast dissolving tablets was carried out with paddle type in USP dissolution apparatus at rpm 50 and temperature 37±0.5°C in 0.5% SLS in water. At each specified intervals of time 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by UV spectroscopy method at wavelength of 345.5 nm.

Details of dissolution test:

Dissolution test apparatus: USP type II
Speed : 50 rpm
Stirrer : Paddle type
Volume of medium : 900 ml
Volume withdrawn : 5 ml
Medium used : 0.5% SLS in distilled water
Temperature : 37±0.5ºC

3. RESULTS AND DISCUSSION

3.1. IR of Montelukast sodium

I R of the Montelukast sodium was determined by FTIR spectra. Physical mixture of drug and polymer was characterized by FTIR spectral analysis. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Montelukast sodium were found to be unaltered in the drug- polymer physical mixtures, indicating they were compatible chemically for the best formulation.

The results of Bulk density and tapped density were found in the range of 0.476-0.588 g/cm^3 and 0.555 - 0.714 g/cm^3. The compressibility index was found between 14.9-21.02%. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 24.12° - 29.56°.

Code	Crospovidone+ Sodium starch glycolate	Code	Sodium starch glycolate+ Crospovidone
CS1	1:1	SC1	-
CS2	1:2	SC2	1:2
CS3	1:3	SC3	1:3

Table 1: Preparation of co-processed superdisintegrants different ratios

The results of weight variation of tablets for all formulations were ranged from 847.80±0.603 to 853.2±1.362 (mg) indicating that the weight variation is within the pharmacopoeial limits. Hardness was ranged from 6.2±0.34 to 6.59±0.(kg/cm^2). Friability ranged from 0.0133±0.003 to 0.097±0.0209(%) indicating that the friability of all formulations was less than 1%. thickness of all formulations ranged from 4.11±0.18 to 4.78±0.20 (mm). The percentage drug content of all formulations was ranged from 97.06±0.92 to 100.15±0.52 (%) which was all within the acceptable limits of official standards. Wetting time of all formulations ranged from 39 to 20 sec. Water absorption ratio was found to be ranged from 50.75 to 64.58 and disintegration time was found to be ranged from 53 to 24 sec.

All the FDT formulations were evaluated for their *in-vitro* drug release according to the procedure described in methodology and the results are shown in **table 5**. The maximum drug release of 91.03% was obtained from formulation F9, and minimum drug release of 74.80% shown by F2. The average drug release immediately after dispersion for all the formulations was in the range of 74.80% to 91.03%. The control formulation F1 drug release was found to be 13.3%. The formulation F9 containing co-processed superdisintegrants sodium starch glycolate: crospovidone (1:3) enhanced the dissolution rate of fast dissolving tablets.

The release obeyed first order kinetics and the results of this investigation showed high correlation coefficient among the formulation for first order release and the probable release mechanism was initial diffusion and the value of release exponent (n) was found to be a function of the polymer used and the physicochemical properties of the drug molecule itself and the n values was found to be in the range of 0.113 to 0.348 followed with Fickian (case I) release.

Formula code	F1 (CPO)	F2 (1:1)	F3 (1:2)	F4 (1:3)	F5 (1:1)	F6 (1:2)	F7 (1:3)	F8 (1:2)	F9 (1:3)	F10 (1:2)	F11 (1:3)
Montelukast sodium	10	10	10	10	10	10	10	10	10	10	10
Co-processed superdisintegrants	-	6	6	6	6	6	6	6	6	6	6
Mcc	30	30	30	30	30	30	30	30	30	30	30
Mannitol	101	95	95	95	95	95	95	95	95	95	95
Sodium saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3
Total weight	150	150	150	150	150	150	150	150	150	150	150

Table 2: Formulation development montelukast sodium fast dissolving tablets

Code	Bulk density g/cc	Tapped density g/cc	Carr's index%	Hausner's ratio	Angle of repose(°)
F1	0.526±0.094	0.666±0.120	21.02±0.03	1.26	29.56±0.04
F2	0.526±0.101	0.666±0.034	21.02±0.094	1.26	29.19±0.067
F3	0.588±0.074	0.714±0.069	17.64±0.065	1.21	27.89±0.051
F4	0.555±0.089	0.666±0.091	16.6±0.074	1.2	26.21±0.079
F5	0.476±0.093	0.588±0.113	19.04±0.093	1.23	27.97±0.084
F6	0.476±0.112	0.555±0.108	14.23±0.034	1.16	27.61±0.099
F7	0.5±0.107	0.588±0.07	14.9±0.107	1.17	25.52±0.021
F8	0.526±0.099	0.666±0.074	21.02±0.099	1.26	25.86±0.044
F9	0.5±0.094	0.625±0.043	20.0±0.102	1.25	24.12±0.042
F10	0.5260.067	0.666±0.021	20.02±0.074	1.26	27.61±0.042
F11	0.5±0.086	0.625±0.09	20±0.065	1.25	25.86±0.042

Table 3: Pre-Compression Parameter results

Code	Weight variation (mg)	Hardness kg/cm^2	Thickness	Friability (%)	Drug content (%)	Disintegration Time (sec)	Wetting time	Water absorption ratio
F1	149.91±0.22	2.72±0.10	3.12±0.01	0.38±0.15	93.51±0.57	240	55	39.95
F2	149.83±0.36	2.9±0.09	3.15±0.03	0.76±0.11	95.92±0.42	40	36	50.8
F3	150.21±0.49	3.16±0.04	3.15±0.03	0.77±0.09	96.75±0.32	49	39	57.8
F4	150.92±0.41	3.32±0.007	3.14±0.02	0.90±0.62	97.5±0.27	53	36	55.84
F5	150.16±0.32	3.15±0.05	3.14±0.01	0.41±0.44	96.20±0.89	30	32	59.42
F6	149.95±0.91	3.37±0.03	3.15±0.04	0.92±0.53	96.85±0.42	33	34	55.18
F7	150.51±0.99	3.06±0.10	3.12±0.01	0.37±0.20	96.57±0.84	39	33	59.65
F8	150.60±0.60	3.14±0.14	3.14±0.02	0.40±0.32	97.87±0.42	28	28	62.08
F9	150.01±0.59	3.05±0.05	3.14±0.01	0.18±0.06	98.79±0.42	24	20	64.58
F10	150.51±1.02	3.27±0.06	3.15±0.01	0.33±0.09	97.31±0.16	29	31	50.75
F11	150.03±0.59	3.16±0.04	3.14±0.01	0.66±0.09	95.74±0.57	31	30	54.45

Table 4: Post-Compression Parameter results

Sl.no	Time in mins	% Cumulative Drug Release											
		Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	MP
1	0.5	5.4	31.5	36.5	39.5	39	39.75	37.75	45.25	46.25	40.25	44.75	34.25
2	1	6.0	59.42	59.45	56.96	51.96	49.47	51.95	54.50	56.50	53.47	52.74	47.44
3	1.5	6.57	65.0	68.28	68.28	63.25	60.74	57.99	70.80	73.31	67.76	69.79	59.70
4	2	7.07	68.11	73.15	71.91	70.6	68.07	65.56	75.94	80.72	73.64	72.92	65.28
5	3	7.53	70.23	75.3	76.05	73.24	72.70	70.92	79.60	83.66	75.54	78.32	70.14
6	4	9.67	72.36	76.97	77.47	75.39	75.35	72.31	82.54	85.12	78.45	81.25	76.02
7	6	10.9	73.26	78.13	78.39	78.05	77.00	74.95	84.74	87.08	80.38	83.69	80.43
8	8	12.0	73.90	79.06	78.56	79.97	78.42	76.61	86.95	89.05	82.32	84.89	82.87
9	10	13.3	74.80	80.23	78.73	81.90	79.59	77.77	88.16	91.03	84.01	85.60	85.07

Table 5: *In-vitro* drug release studies

Formula code	Koresmeyar and Peppas		Higuchi	Hixon Crowel	First order	Zero order
	R^2	N	R^2	R^2	R^2	R^2
F1	0.967	0.348	0.981	0.975	0.975	0.973
F2	0.635	0.130	0.559	0.492	0.534	0.414
F3	0.706	0.122	0.62	0.557	0.604	0.468
F4	0.746	0.113	0.632	0.539	0.572	0.473
F5	0.849	0.129	0.773	0.722	0.769	0.627
F6	0.869	0.128	0.780	0.704	0.740	0.630
F7	0.868	0.127	0.794	0.723	0.760	0.647
F8	0.855	0.119	0.769	0.739	0.797	0.623
F9	0.828	0.117	0.730	0.711	0.779	0.582
F10	0.823	0.126	0.738	0.692	0.744	0.589
F11	0.855	0.119	0.765	0.713	0.760	0.616
F12	0.772	0.164	0.717	0.653	0.696	0.565

Table 6: Release exponent values and release rate constant values for different formulation

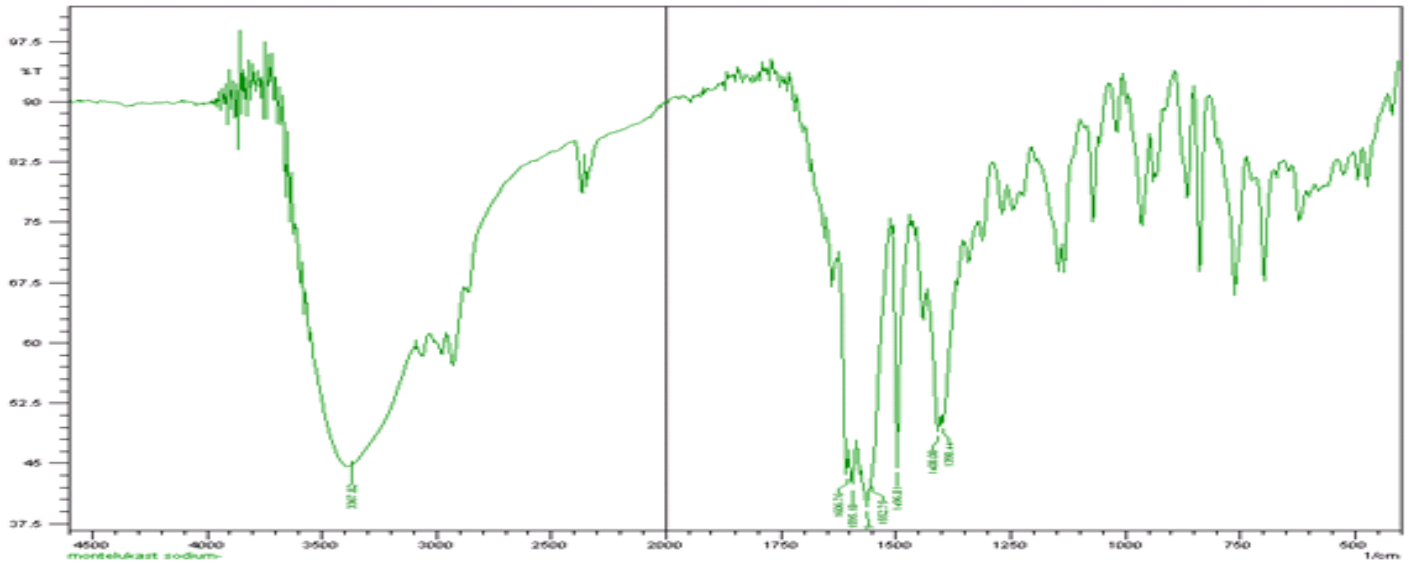

Figure 1: IR spectrum of Montelukast sodium

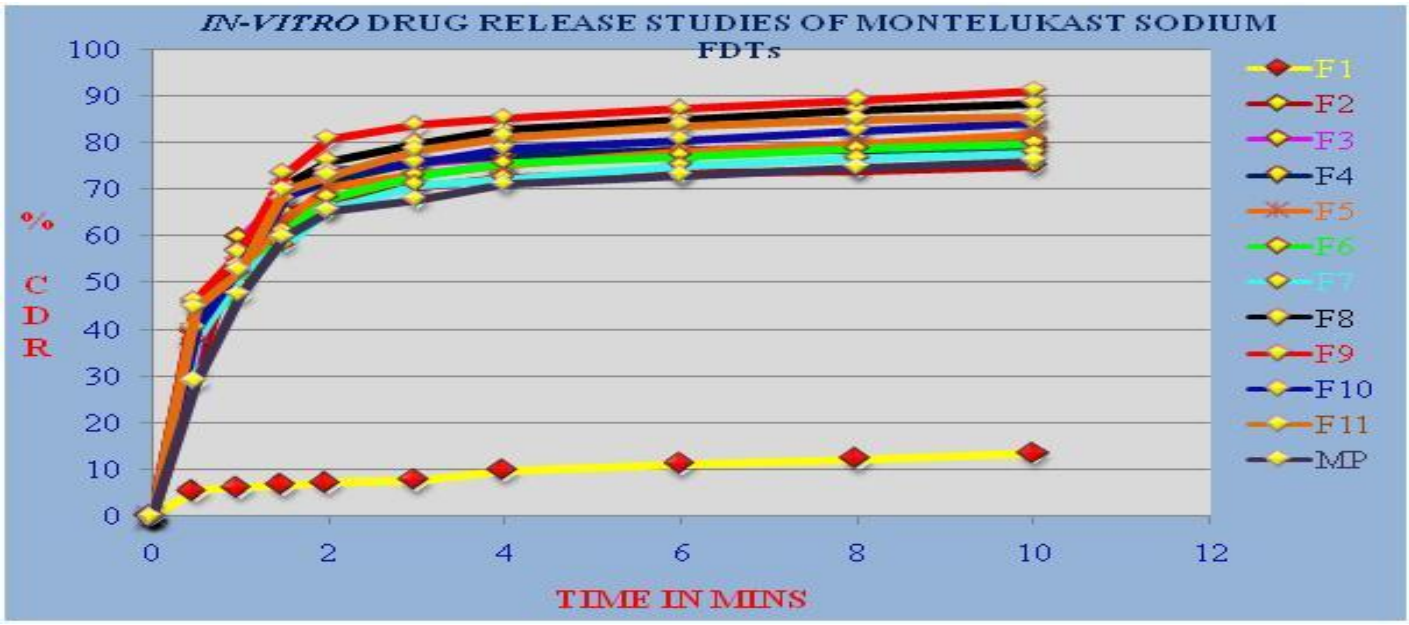

Figure 2: *In-vitro* release of Montelukast sodium FDTs with marketed product

3.2. Stability studies

Stability study was conducted for two best formulations selected based on *in-vitro* disintegration time and *in-vitro* drug release. There was no significant reduction in drug release profile of formulation F9 no significant taste, color and odor changes**.** There was no significant variation in the drug content and *in-vitro* dissolution profiles after two months stability study for best formulations F9 thus specialized packing and storage conditions are necessary for the prepared fast dissolving tablets of Montelukast sodium.

4. SUMMARY

It can be summarized that stable Montelukast sodium fast dissolving tablets were prepared successfully by using co-processed superdisintegrants by direct compression method to enhance the dissolution rate.

5. CONCLUSION

The fast dissolving tablets of Montelukast sodium was successfully developed and evaluated. The F9 formulation containing sodium starch glycolate and

crospovidone in 1:3 ratios was found to have the higher percentage of drug release compared with other formulations. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and sodium starch glycolate are superior to physical mixture of crospovidone and sodium starch glycolate used in Montelukast sodium fast dissolving tablets by direct compression method. The Montelukast sodium FDTs were found to have enhanced dissolution rate. Stability studies of the tablets in normal humidity conditions were checked and observed that FDT preparations require specialized packing and storage conditions.

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Conflict of Interest: None Declared

