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Formulation and evaluation of oral disintegrating tablets of montelukast sodium: effect of functionality of superdisintegrants

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ABSTRACT

Montelukast sodium is a potent, selective and orally acting leukotriene receptor antagonist that acts by inhibiting physiological actions of the cysteinyl leukotrienes(LTC4,LTD4and LTE4) . It is used in the prophylaxis and treatment of asthma. As precision of dosing and patient's compliance become important prerequisite for asthma management, there is a need to develop formulations for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's acceptability. Hence in the present study an attempt has been made to prepare fast disintegrating tablets of Montelukast sodium in the oral cavity with enhanced dissolution rate. The tablets were prepared with three superdisintegrants i.e polyplasdone XL10,Ac-Di-Sol and Primojel. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, Compressibility index and Haussner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 9sec. Based on dissolution rate the disintegrants can be rated as Polyplasdone XL10 > Ac-di-sol > Primojel. Hence polyplasdone XL10 was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of Montelukast sodium. All the dissolution parameters were calculated and compared with market tablet. An increase in the dissolution rate was observed with M8 formulation when compared to market one. It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using super disintegrants.

Keywords: Oral disintegrating tablets, Direct compression, cysLT, Leukotriene receptor antagonist.

INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in design of dosage forms. Tablet is most popular among all dosage forms existing today because of convenience of self administration, compactness and easy manufacturing. However many patients, especially elderly find it difficulty in swallowing tablets, capsules, fluids and thus do not comply with prescription which results in high incidence of non-compliance and in-effective therapy[1]. Patient convenience and compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Rapidly disintegrating / dissolving tablet is one of such example, for the reason of rapid disintegration or dissolution in mouth with saliva[2-4]. Significance of this drug delivery system includes administration without water, accuracy of dosage forms, ease of portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and rapid onset of action[5-7].

Montelukast sodium [8-12] is chemically designated as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid, monosodium salt, an orally administered drug of choice in the treatment of asthma in adults and children.

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Other problems like hand tremors, dysphagia incase of geriatric and non co-operative patients the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these drawbacks Mouth dissolving tablets or orally disintegrating tablets or Fast dissolving tablets has emerged as an alternative oral dosage form.

In the present study an attempt had been made to prepare rapidly disintegrating 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 mouth dissolving tablets is the use of super disintegrants like polyplasdone, Ac-di-sol , Primojel, which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. These systems may offer superior profile with potential mucosal absorption thus increase the drug bioavailability.

These systems are also called melt-in-mouth tablets, Reprimelts , porous tablets, Orodispersible , quick dissolving or rapidly disintegrating tablets.

EXPERIMENTAL

Materials and Methods:

Montelukast sodium (obtained as gift sample from Cadila

pharmaceuticals limited,Dholka, Ahmedabad) Pearlitol SD200, Polyplasdone XL10,Ac-Di-Sol,Primojel,colloidal silicon dioxide, Magnesium stearate, Peppermint flavour, Acesulfame potassium, Ferric oxide(Red),Aspartame used were of Pharmacopoeial grade.

Estimation of Montelukast sodium:

An UV Spectrophotometric method based on the measurement of absorbance at 350 nm, stock prepared in methanol and further dilutions in distilled water were used in the estimation of Montelukast sodium. The method obeyed Beer's law in the concentration range of 0-10µg/ml. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of Montelukast sodium content in various products and in vitro dissolution studies. The result was shown in **Fig.1**

Preparation of Mixed Blend of Drug and Excipients:

All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from each specified formulation (depicted in the **Table 2**) and all the ingredients were co ground in a mortar and pestle. The powder blend was evaluated for flow properties as follows and the result is given in the **Table 1**.

Angle of Repose:

Angle of repose was determined using funnel method[13]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (?) was calculated using the formula:

$$q = \tan^{-}[h/r]$$

Bulk density:

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\rho_b = M/V_b$$

Tapped density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula:

$$\rho_t = M/V_t$$

Compressibility index:

Compressibility index I is calculated as follows:

$$I = V_0 - V_t / V_0 \times 100$$

Where V_0 is the bulk volume
V_t is the tapped volume.

The value below 15%indicates a powder with usually give rise to good flow characteristics where as above 25% indicate poor flowability.

Haussner's ratio:

Haussner's ratio[14] is an indirect index of ease of powder flow. It is calculated by the following formula

Haussner's ratio = ρ_t/ρ_b

ρ_t = tapped density

ρ_b = bulk density

Lower Haussner's ratio (<1.25) indicates better flow properties than higher ones(>1.25)[15]

Compression of tablets:

The ingredients depicted in **Table 2** (except Talc & Magnesium stearate) were mixed homogenously and co ground in a mortar and pestle. Finally talc and Magnesium stearate were added and mixed for 5min.The mixed blend of drug and excipients was compressed using a single punch CADMACH punching machine to produce round tablets weighing 200mg with a diameter of 9mm. A minimum of 50 tablets were prepared for each batch.

EVALUATION OF TABLETS:

All the prepared tablets were evaluated for the following parameters as per USP guidelines and the results are given in the **Table 3**.

Weight variation:

Twenty tablets were randomly selected from each batch, individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Hardness:

Hardness or tablet crushing strength (F_c); the force required to break a tablet in a diametric compression was measured using a PFIZER tablet hardness tester.

Tensile strength:

Tensile strength of tablets was calculated using the following formula:

$$T = 2F_c / d\,t.$$

where F_c- crushing strength, d- diameter, t-thickness of tablet.

Table 1: Evaluation of Directly Compressible Blend

Parameter	M1	M2	M3	M4	M5	M6	M7	M8	M9
Angle of repose(θ)	32	29	33	32	30	31	34	33	34
Bulk density(gm/cm^3)	0.54	0.58	0.54	0.58	0.55	0.53	0.59	0.57	0.58
Tapped density(gm/cm^3)	0.63	0.71	0.66	0.67	0.69	0.65	0.73	0.67	0.68
% Compressibility	13	18	14	12	18	11	19	14	17
Haussner's ratio	1.16	1.21	1.20	1.13	1.17	1.15	1.22	1.18	1.19
Flow ability	Good	Good	Good	Good	Good	Good	Good	Good	Good

Friability:

Friability of tablets was determined using Roche friabilator (USP).Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed. Percent friability = [initial wt- final wt/ initial wt] × 100.

Drug content uniformity:

The drug content was determined by taking the powder equivalent to 10mg, then it was dissolved in distilled water and absorbance was taken against the blank at 350 nm.

Invitro Disintegration time:

The disintegration test was performed using an IP 85 disintegration apparatus with distilled water at 37± 0.5°C.

In vivo disintegration time:

The time required for tablets to disintegrate in the mouth cavity was determined by holding the tablets in the mouth. The subjects were instructed to gently move the tablet against the upper part of the mouth with the tongue. It is emphasized to the subject that this is a gentle motion with no biting of the tablet. Immediately after the last noticeable particle was disintegrated, the time was again recorded. Test was conducted in duplicate and average time is reported. The test was performed in five healthy human volunteers in the age group of 23 to 28 years.

In vitro dispersion time:

Tablet was added to 10 ml of Distilled water at 37± 0.5°C time required for complete dispersion of a tablet was measured.

Measurement of liquid uptake (Wetting time):

A glass petridish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.

Water absorption ratio:

A piece of tissue paper was folded twice was placed in a small petridish containing 6ml 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, R was determined using the following equation:

$$R = 100 \times W_a - W_b / W_b$$

where $W_{b\,is}$ weight of tablet before water absorption and W_a is weight of tablet after water absorption.

Dissolution rate studies:

Dissolution rate of Montelukast sodium from all formulations was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of Distilled water with 0.5% SLS a speed of 50rpm & a temperature of 37±0.5°C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filler of 0.45µm at different time intervals, suitably diluted and assayed for Montelukast sodium by measuring absorbance at 350 nm. The dissolution experiments were conducted in triplicate and the results are shown in the **Fig.2**

RESULTS AND DISCUSSION:

Nine set (M1-M9) of tablet formulations were prepared and evaluated accordingly. The composition of tablets is presented in table 1. Different concentrations of Superdisintegrants (5%, 7.5%, and10%) were investigated. Drug load (5%) was maintained steady for all the formulations. The final blend of drug and excipients were evaluated for flow properties and was found that the flow property of prepared powdered blend was good and the result is given in the **table 1.** All the obtained formulations exhibited satisfactory tablet characteristics as discussed in **Table 3**.

The disintegration time in relation to superdisintegrant concentration is shown in **Fig.3** reflecting that the optimum concentration rapid will be the disintegration. The disintegration time for each batch tablet was found to be less than one minute and the tablets containing polyplasdone (M7,M8 and M9) showed lowest disintegration time. All the QC parameters of formulations were complied with the official specifications with drastic decrease in disintegration time and the result is given in the **Table 3**. The wetting time for all the formulations was within the range (15-22sec).The lowest (15sec) was obtained with formulation M8. All the tablets released almost 70% of the drug within 10 min (**Fig. 4**) proving its fast dissolving action.

Table 2: Formulae of Fast Dissolving Tablets of Montelukast sodium

Ingredient	M1(%)	M2(%)	M3(%)	M4(%)	M5(%)	M6(%)	M7(%)	M8(%)	M9(%)
Montelukast sodium									
eq.to Montelukast	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4
Pearlitol SD 200	160.58	155.58	150.58	160.58	155.58	150.58	160.58	155.58	150.58
Primojel	10	15	20	_	_	_	_	_	_
Ac-di-Sol	-	-	—	10	15	20	_	_	_
PolyplasdoneXL10	—	—	—	_	_	_	10	15	20
Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2
Magnesium stearate	6	6	6	6	6	6	6	6	6
Acesulfame potassium	8.6	8.6	8.6	8.6	8.6	8.6	8.6	8.6	8.6
Ferric oxide(Red)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Peppermint flavor	2.17	2.17	2.17	2.17	2.17	2.17	2.17	2.17	2.17

Table 3: Evaluation of Formulations

Parameter	M1	M2	M3	M4	M5	M6	M7	M8	M9
Average weight(mg)±S.D	207±0.2	206±0.32	205±0.32	208±0.24	205±0.36	205±0.36	207±0.34	207±0.34	208±0.24
Hardness(kg/cm^2) ±S.D	3±0.12	3.5±0.34	3.5±0.34	3±0.22	3±0.25	3±0.25	3±0.32	3.5±0.32	3±0.31
Tensile strength(kg/cm^2)	9.55±0.12	9.67±0.86	12.92±0.76	9.72±1.28	9.87±0.92	9.56±0.69	10.66±0.45	9.68±0.28	10.32±0.66
Friability (%)	0.19	0.21	0.18	0.17	0.20	0.19	0.18	0.16	0.16
InvitroDisintegration time(sec)	21	20	19	18	18	17	14	11	15
Drug content (%)	92	93	90	92	93	91	93	99	94
Invitro dispersion time(sec)	22	22	18	19	17	16	14	12	14
Invivo disintegration time(sec)	15	14	12	14	14	13	11	9	11
Wetting time(sec)	22	22	21	19	20	18	19	15	17
Water absorption ratio(R)	57	54	60	56	61	58	59	52	55

Table 4: Correlation Coefficient(R) Values of Oral disintegrating Tablets of Montelukast sodium Formulated Employing Different Super disintegrants as per Zero Order and First Order Kinetics

Parameter	M1	M2	M3	M4	M5	M6	M7	M8	M9	Marketed
Zero order(r^2)	0.8681	0.8176	0.8611	0.8153	0.8493	0.8579	0.8589	0.8599	0.8611	0.8768
First order(r^2)	0.9411	0.9511	0.9137	0.9637	0.9524	0.9657	0.9524	0.9957	0.9637	0.9726

Table 5: Dissolution Parameters of Montelukast sodium tablets

Parameter	$t_{(10)}$(sec)	$t_{(50)}$(sec)	$t_{(90)}$(min)	DE_5(%)	K_{min}^{-1}
M1	12	48	>10	54	0.231
M2	12	42	>10	60.2	0.276
M3	12	42	>10	60.1	0.276
M4	12	48	>10	60.7	0.243
M5	12	42	>10	66.8	0.276
M6	12	42	>10	64.2	0.276
M7	12	48	>10	61.8	0.253
M8	12	36	7min42sec	70.1	0.356
M9	12	42	9min48sec	63	0.276
Marketed	18	54	>10	48.3	0.230

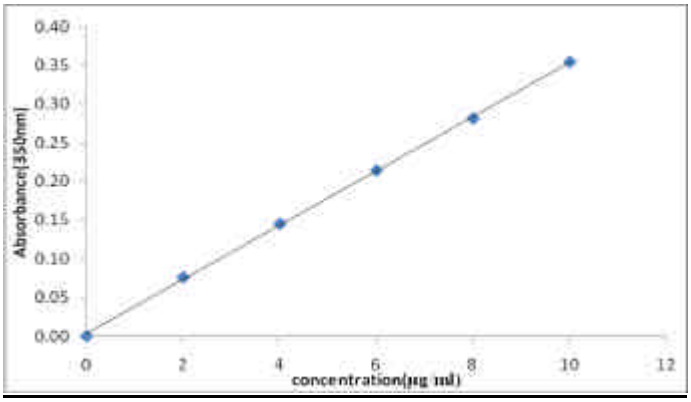


Figure : 1: calibration curve of Montelukast sodium

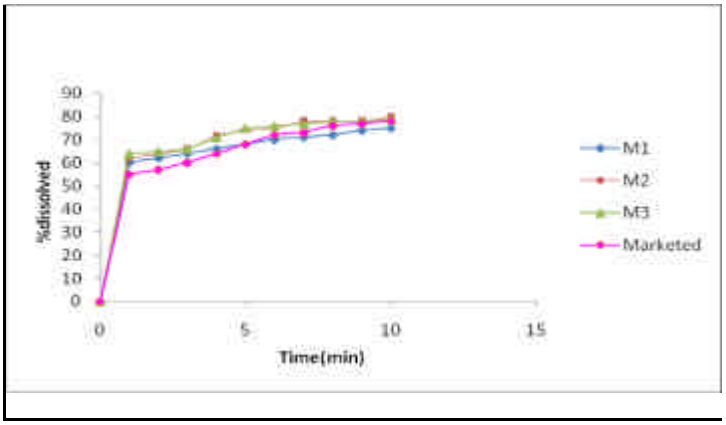


Figure : 2(a): Effect of primojel level on the release of Montelukast sodium.

M1: 5% Primojel M2: 7.5% Primojel M3: 10% Primojel

Dissolution profiles were shown in **Fig. 4** and dissolution parameters for all batches were summarized in **Table 4**. Analysis of dissolution data as per zero order and first order kinetic models based on correlation coefficient (r^2) values (**Table 4**) indicated that the dissolu-

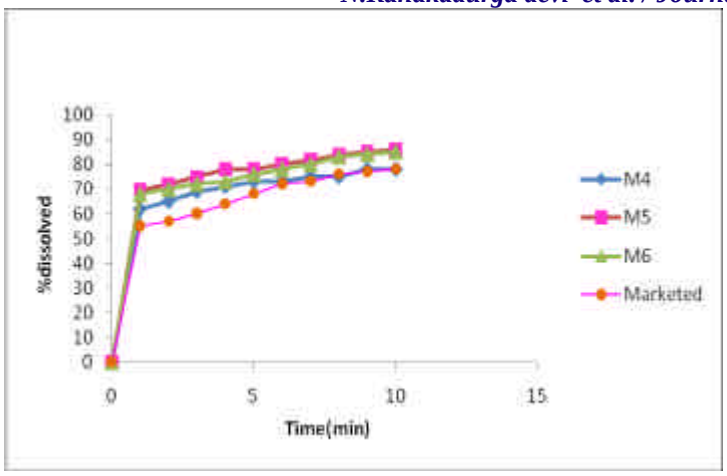


Figure 2 (b):Effect of Ac-Di-Sol level on the release of Montelukast sodium.

M4:5% Ac-Di-Sol M5:7.5% Ac-Di-Sol M6:10% Ac-Di-Sol

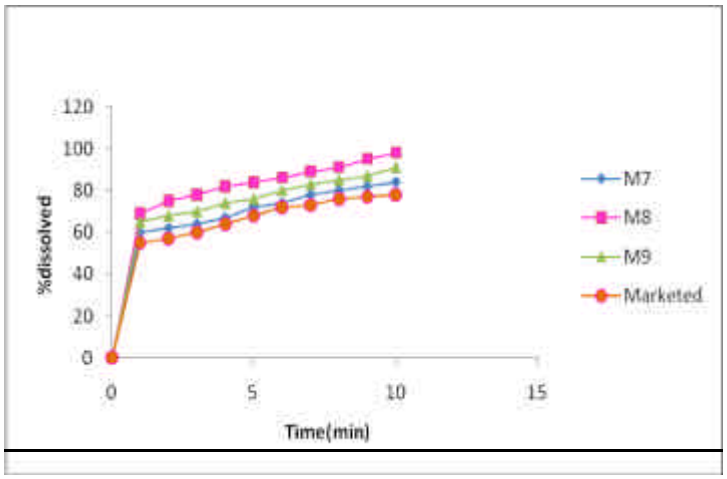


Figure : 2(c): Effect of Polyplasdone XL 10 level on the release of Montelukast sodium

M7: 5% Polyplasdone XL 10 ;M8:7.5% Polyplasdone XL 10 ;M9:10% Polyplasdone XL 10

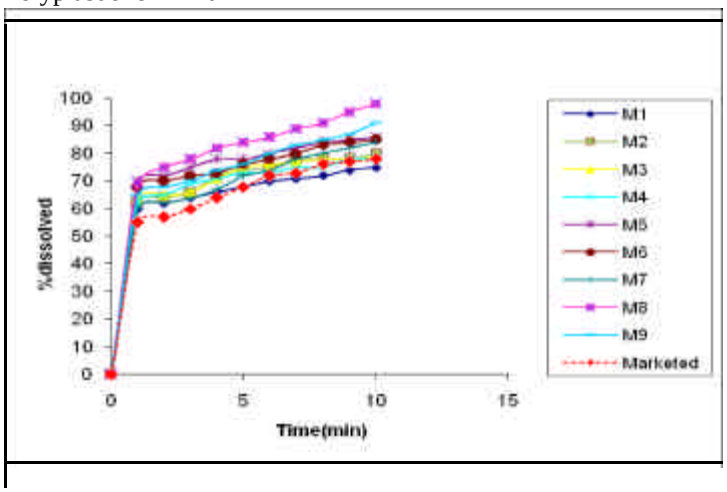


Figure 2: Dissolution profiles of oral disintegrating tablets of Montelukast sodium

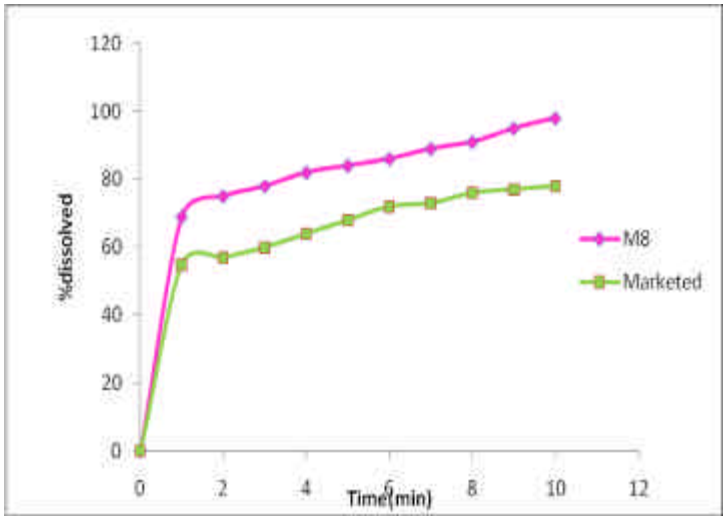


Figure3 : Comparision of dissolution profiles of optimized formula(M8) with Marketed product.

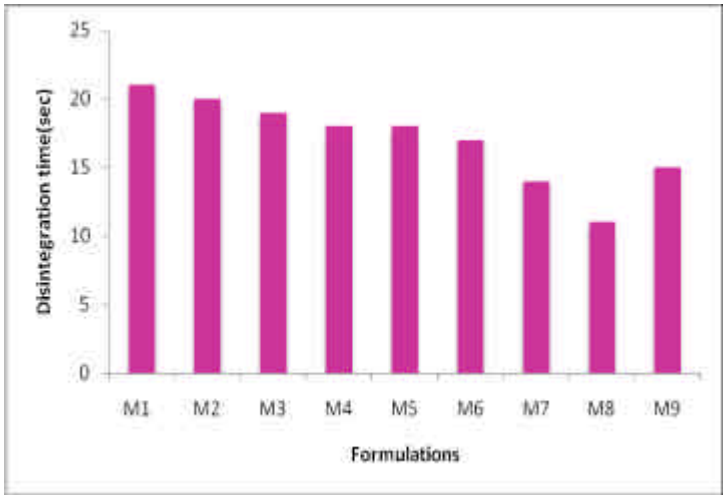


Figure 4: Effect of superdisintegrants on disintegration time of oral disintegrating tablets of Montelukast sodium

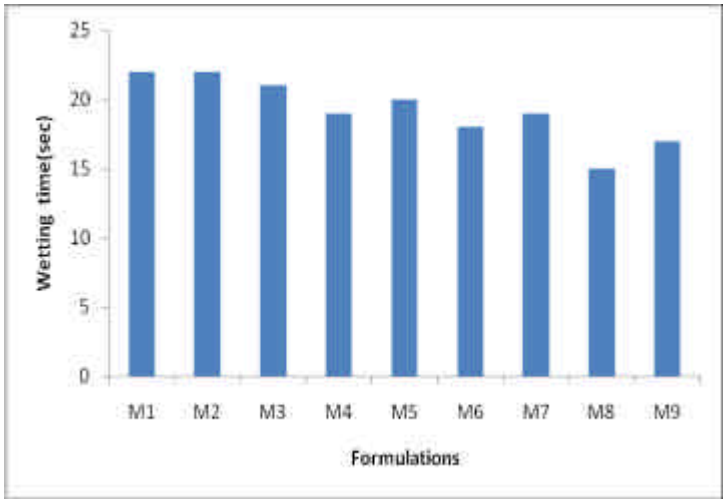


Figure 5: Effect of superdisintegrants on Wetting time of oral disintegrating tablets of Montelukast sodium

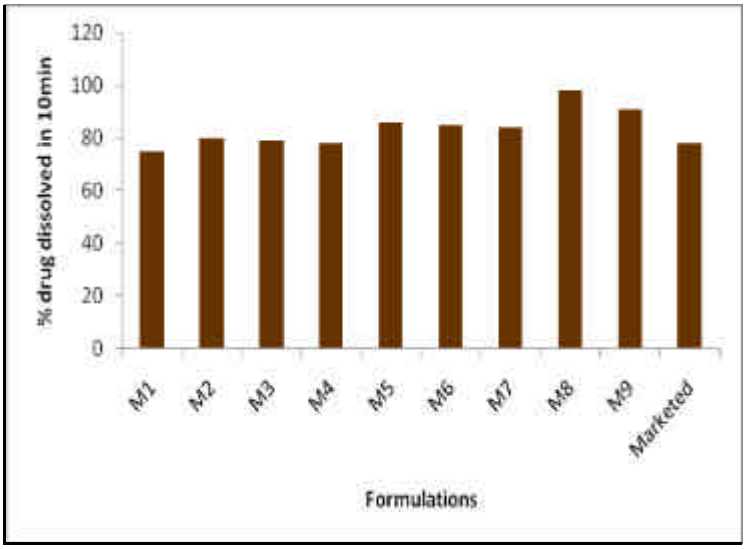
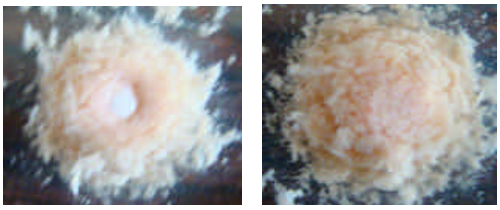


Figure 6: Percent Drug Dissolved in 10minutes from Montelukast sodium Tablets

A: 0 time B: 2 sec C: 5 sec



D: 8 sec E: 11 sec

Figure 7: Photographs showing disintegration of M8 tablet.

tion of Montelukast sodium from all the tablets followed first order kinetics. Among all the formulated tablets M8 which is based on Montelukast sodium with 7.5% Polyplasdone gave the highest dissolution (99%) in 10 mins. Based on dissolution rate the disintegrants can be ranked as PolyplasdoneXL10 > Ac-di-sol> Primojel. Polyplasdone XL10 showed better dissolution and dissolution efficiency (DE_5%) among the disintegrants studied at three levels (5%, 7.5% and 10%). Hence Polyplasdone XL10 was recommended as suitable disintegrant for the preparation of directly compressible mouth dissolving tablets of Montelukast sodium as these are a very good alternative drug delivery to geriatric and paediatric patien

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