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PREPARATION AND EVALUATION OF MELT-IN MOUTH SUBLINGUAL TABLETS OF MONTELUKAST SODIUM

Alaa Eldin A. Kassem[1], Maha A. Marzouk[2], Sheren A. El-Adawy[2] and Aya M. Dawaba[2*]

[1]Department of Pharmaceutics, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo 11651, Egypt.
[2]Department of Pharmaceutics, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo 11651, Egypt.

ABSTRACT

Montelukast Sodium is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. Montelukast Sodium has oral bioavailability of 64% due to hepatic first pass metabolism and has a short half-life of 5.5 hr. The present work was an attempt to develop and evaluate melt-in mouth sublingual tablets of Montelukast Sodium which can reduce the frequency of dosing and improve bioavailability. These melt-in mouth sublingual tablets were prepared by direct compression methods. These melt-in mouth sublingual tablets were prepared by direct compression methods. The IR and DSC studies show no interaction between drug and polymer or with other additives. Satisfactory results were obtained when subjected to quality control tests of the prepared tablets were done. The stability studies conducted for a period of 6 months showed no appreciable change in drug content. Tablet containing Crospovidone: Ac-Di-Sol (3:1) showed optimum performance against all other prepared formulations. The mean relative bioavailability of the chosen Montelukast Sodium tablet compared to the commercial product (Kokast) was 154.8%. the melt-in mouth sublingual tablet of Montelukast Sodium with improved bioavailability was established.

Key words: *Montelukast Sodium - melt-in mouth sublingual tablets (MMST) - Crospovidone:Ac-Di-Sol.*

INTRODUCTION

Sublingual delivery is well documented in the literature [1-3]. The main use for the sublingual route of drug administration is to provide a rapid onset of action of potent drugs. Some researchers believe that sublingual administration would allow men to get results at a lower dosage than when a tablet is swallowed whole. It can also avoid first-pass metabolism by the liver and is not affected by food [4].

Sublingual route is systemic rather than portal; therefore, hepatic first pass elimination can be avoided, also they avoid the problems of gastrointestinal incompatibility of certain drugs, as well as drug liver uptake and they offer potential for a more rapid absorption and a quicker onset of drug action [5-7].

In some cases, this route may be as effective as intravenous, providing a safer and more comfortable alternative for the patient permitting the use of pharmacologically potent drugs with short biological half-lives; offering convenience, ease of application and localization of their action. Disintegrant addition technique is one of the popular techniques for formulating mouth dissolving tablets because of its easy implementation and cost effectiveness [8].

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper responsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations, severity of asthma and response to treatment [9, 10]. Acute symptoms of asthma usually arise from bronchospasm and require respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyper responsiveness, which enhances susceptibility to broncho-spasm [11].

Montelukast Sodium (MS) is used in prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older, and prevention of

Corresponding Author :- **Aya Mohamed Dawaba** Email:- aya.dawaba@yahoo.com

exercise-induced broncho-constriction in patients 15 years of age and older. Also used in the relief of symptoms of allergic rhinitis [12-14]. MS is extensively metabolized in liver and is excreted through bile so the known drawback of per oral delivery of MS is that it undergoes hepatic first pass metabolism. Thus it shows plasma or biological half-life of 5.5 hr, thereby limiting bioavailability up to nearly 64%.

The important characteristics of tablet formulations used for sublingual delivery are short disintegration and dissolution times [15]. However, to achieve optimal sublingual delivery, properties of the active compound and other properties of the formulation have to be considered. The parent compound has to be soluble, stable, and easily permeable through the mucosal barrier at the administration site. Furthermore, the dosage form has to be rapidly dissolved at the administration site [16].

To demonstrate the feasibility of delivering a drug via the sublingual route, suitable in vivo models must be used to assess the delivery potential in clinical studies. A rabbit model for investigating sublingual drug absorption was established yielding results consistent with clinical data reported in the literature. The sublingual mucosa of both the rabbit and human is none keratinized, and delivery to the rabbit sublingual cavity presents an opportunity to correlate intraoral absorption in man [17].

Present research work was attempted to formulate MS using different combinations of superdisintegrants (namely crospovidone and Ac-Di-Sol) by direct compression technique. However, there is currently no commercially available dosage form for the sublingual delivery of MS. Thus, it would be valuable to develop a sublingual MS delivery system to increase its bioavailability, decrease the administrated dose, and attain a rapid onset of action.

MATERIALS AND METHODS

Materials

Montelukast Sodium (MS) was a gift sample from EEPI Company, Alexandria, Egypt (PubChem CID: 23663996). Cross linked carboxymethylcellulose sodium (Ac-Di-Sol; PubChem CID: 6328154), Mannitol, supplied from El-Nasr pharmaceuticals company, Cairo, Egypt (PubChem CID: 6251). Magnesium stearate was kindly supplied by El-Qahera pharmaceuticals company, Cairo, Egypt (PubChem CID: 5281). Crospovidone (Polyplasdone XL-10; PubChem CID: 6917) were supplied by Medical Union Pharmaceutical (MUP), Cairo, Egypt.

Methods

Compatibility Study between MS and the Selected Polymers

FT-IR spectroscopy

The FT-IR of pure drug and other excipients was measured using Fourier Transform Infra-Red Spectrophotometer (model Impact 410, Milwaukee, WI, USA.). Pure drug and other excipients were separately mixed with IR grade KBr and converted into KBr pellet by hydraulic press and scanned over a range of 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of drug, excipients and combination of both were carried out using Differential Scanning Calorimeter (Shimadzu DSC TA-50 ESI, Japan).The samples were heated from 50 to 450 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.

Preparation of MS melt in mouth sublingual tablets:

Tablets containing MS were formulated using different combinations of superdisintegrants (namely crospovidone and Ac-Di-Sol) and the overall combinations represent 7 %W/W from the final tablets weight as shown in table 1.The tablets were prepared by direct compression technique where all the ingredients were passed through #60 prior to mixing MS and mixture of Superdisintegrants were mixed for 10 min. using mortar and pestle. Following that, the calculated amount of Mannitol was added to the above mixture and blended together for additional 10 min. to obtain a uniform blend. The blend was further lubricated with Magnesium stearate for 5 min. The blend was compressed into tablets with an average weight of 200 mg using an 8 mm flat punch in a single punch tablet press machine (Erweka, Type EK: 0, Erweka apparatus, Frankfurt, Germany).

Evaluation of MS tablets

Uniformity of weight

This test is done by sampling and weighing 6 tablets at random and average weight is calculated. The mean and standard deviation were determined [18]. The results are shown in table 2.

Thickness

The thickness of the tablets was determined using a Micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm [19].

Hardness Test

Hardness of three randomly selected tablets from each formulation (F1 to F6) was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (Tablet hardness tester, Model T H-16, China) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in Kg/cm^2 [20].

Friability Test

Six tablets from each batch were examined for friability using Tablet Fribillator (Model: F T-2D, VEEGO, Progressive Instruments, Bombay, India.) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighed and % friability was calculated [21].

Drug Content

Six tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 60mg of MS was weighed and dissolved in 100ml of pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, The absorbance was measured at wavelength 342nm using UV-Visible spectrophotometer (Spectrophotometer, Jenway Ltd, Model 6105 UV/Vis Felsted, United Kingdom) [22].

Wetting Time

Ten 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 center of the petri dish and the time required for water to reach the upper surface of the tablet was noted as the wetting time.

Test for dispersion

Two tablets were placed in 100 ml of water and stirred gently until it was completely dispersed and smooth dispersion was obtained. The dispersed liquid was passed through sieve no. 22. No residue should remain over the sieve [22].

In Vitro Disintegration Time

The disintegration time for sublingual tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes of the disintegrator (Tablet disintegration test apparatus, VEEGO, Model: VTD-3D, India) and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time [22].

In-vivo disintegration time

The study was designed to determine the disintegration time of MS tablets in the buccal cavity. All volunteers were asked to rinse their mouth with distilled water. Tablets were randomly administered to 3 healthy male volunteers aging (26-35) years at 1 hour time intervals. Tablets were placed under their tongues and the time required for the complete disintegration of the tablets in the oral cavity was recorded using stop-watch and then the mean value was calculated. They were allowed to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable granule had disintegrated, the time was recorded. Moreover, all the subjects were asked to give an evaluation of the samples by answering questions related to taste, comfort, grittiness of the dispersion soon after the tablet got disintegrated and sensation after administration, using a score: 0 (very satisfied), 1 (quite satisfied), 2 (not satisfied) and 3 (not at all satisfied) 23, 24]. The parameters for comfort included convenience of administration, quickness of disintegration and suitability of pharmaceutical form for taking without water. Sensation was evaluated considering residues left in the mouth after administration. The subjects were asked to spit out the content of the oral cavity after tablet disintegration and rinse their mouth with distilled water. The swallowing of saliva was prohibited during the test, and also saliva was rinsed from the mouth after each measurement [25].

In-Vitro Dissolution Testing

Dissolution study was conducted for all the formulation using USP type-I apparatus (DrSchluriger (Dis 6000), Switzerland). The dissolution test was performed using 300ml of phosphate buffer (PH 6.8), as the dissolution medium at 50 rpm and 37°C±0.5°C. Three milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 342nm [19].

Accelerated Stability Testing

The stability study was established by the ICH guidelines and the best formulae of sublingual tablets of MS were subjected to degradation reactions. Where, enough number of tablets of MS selected formulae were stored in desiccators in which saturated solution of sodium chloride were placed to maintain 75% relative humidity. The desiccators were stored in two thermostatically controlled hot air ovens at 30°C and 40°C for 180 days. The drug content of the stored formulae, at each temperature, was evaluated according to the method of assay, periodically at15, 30, 60, 90 and 180 days. Results were compared with the zero time (pre-storage) data.

Bioavailability study

Albino rabbits were utilized to investigate the bioavailability parameters for the chosen prepared sublingual tablet compared to the commercial product (Kokast®) after their sublingual administration. The study was conducted in accordance with the ethical committee regulations (Approval Code: 106) at Faculty of Pharmacy (girls), Al Azhar University, Cairo, Egypt which comply with the ARRIVE guidelines and carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments. The pharmacokinetic parameters were calculated using the residual method. The

investigated parameters included C_{max}, T_{max}, V_d, $AUC_{0-\infty}$. Also the relative bioavailability of the chosen MS tablet formulation compared to the commercial product (Kokast®) was determined.

Data analysis

Statistical analysis of the experimental work was carried out using ANOVA.

RESULTS

Compatibility Study between MS and the Selected Polymers

Figure (1) shows the infrared spectroscopy of MS and each of the polymers added in preparing sublingual tablets. While the DSC thermograms of MS, polymers were represented in Figure 2.

Post compression Evaluation of MS tablets

The weight of single tablet was targeted as 200 mg and hence the % deviation accepted as per USP 35 is 7.5 %. 10 tablets were selected randomly from all formulae and weighed individually. Average weight was calculated. The weight variation values for all the formulae were found to be within the acceptable limits.

Table (2) shows the different hardness values of different tablet formulae ranged from (5.53-7.16). According to the requirements of USP35, all the prepared tablets complied with the limits of friability. The average MS content of selected sublingual tablets ranged from (89.3-98.3%). Table (3) compiles the average wetting time of prepared sublingual tablets ranged from (17.4-168.2 Sec.). By applying the test for dispersion, it was obvious that all of the prepared tablets passed this test and no residue was found on the sieve. The average disintegration time values in seconds of prepared sublingual tablets were in the range (16.5-150.9) and (12.59–120.33) for the in-vitro and in-vivo respectively, and the ascending order was F5 < F4 < F1 < F2 < F3 < F6.The differences in the in-vitro disintegration time were also confirmed in the in-vivo testing.

In-vitro dissolution studies

In vitro dissolution studies of the prepared sublingual tablets showed that the dissolution rate was found to increase linearly with increasing concentration of superdisintegrant corspovidone. This was marked by decrease disintegration time values for tablet formulation containing higher proportions of crospovidone. Formulation F6 which represented control formula shows drug release that reaches 65% at the end of 720 Sec [24]. The water soluble inert fillers were reported to be used as inert carriers to form a high water soluble dispersion with active agents [34].

Accelerated Stability Testing

The result of the accelerated stability testing of MS sublingual tablet stored at 30°C and 40°C, 75% relative humidity within 180 days. The percent of MS degraded after six months from formula F5 which represents the zero-order kinetics. After the six months storage period, the physiochemical properties of tablets like disintegration time and dissolution rate were found to be within the limits; which proved that MS sublingual tablet were stable at the end of the six months period.

Bioavailability study

Figure 5 showed the time courses of mean rabbit's plasma concentration of MS after sublingual administration of Kokast® and formulation F5. A slow rise in the plasma concentration of Montelukast after dosing with Kokast® tablets till 2 h, where it showed a mean peak plasma concentration 0.9796 µg/ml (C_{max}) and it was reached after 4 h (T_{max}). It was obvious that, the mean plasma peak concentration (C_{max}) of MS after sublingual administration of formulation F5 was found to be 1.798 µg/ml, while T_{max} reached at 1.5 h. The pharmacokinetics parameters were calculated using the residual method [36] and were represented in Table 4.

Table 1.Composition of melt in mouth sublingual tablets of MS

Formulae	MS (%)	Superdisintegrants (7%) Crospovidone:Ac-Di-Sol	Magnesium stearate (%)	Mannitol up to (mg)
F1	5	1 : 1	0.5	200
F2	5	1 : 2	0.5	200
F3	5	1 : 3	0.5	200
F4	5	2 : 1	0.5	200
F5	5	3 : 1	0.5	200
F6	5	-- : --	0.5	200

Table 2. Evaluation of MS tablets prepared by direct compression technique

Formula	Average weight(mg)±SD	Thickness (mm)± SD	Hardness(Kg/cm2)± SD	Friability (%) ± SD	Drug content± SD
F1	197± 1.34	4.33±0.12	5.53±0.18	0.27±0.01	98.3±2.54

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F2	200± 1.33	4.43±0.11	5.602±0.13	0.37±0.012	93.4±1.67
F3	199± 2.54	4.31±0.16	6.12±0.11	0.24±0.014	95.5±0.78
F4	196.2± 1.78	4.37±0.11	6.11±0.14	0.21±0.019	89.3±3.45
F5	193± 1.56	4.40±0.15	5.92±0.12	0.26±0.02	92.6±0.57
F6	205± 2.82	3.89±0.13	7.16±0.103	0.23±0.025	97.5±2.05

Table 3. Evaluation of post-compression parameters of MS sublingual tablets

Formula	Wetting time (Sec.)	Dispersion test	In-vitro disintegration (Sec.) ± SD	In-vivo disintegration (Sec.) ± SD	Sensation comfort score*
F1	38.5±2.9	PASS	32.56±3.33	29.43±2.6	2
F2	44.8±1.98	PASS	43.95±5.48	40.43±3.58	2
F3	52.2±2.38	PASS	50.89±6.47	48.93±4.57	2
F4	22.6±3.31	PASS	21.43±3.48	18.62±2.46	0
F5	17.4±0.84	PASS	16.508±0.78	12.59±1.57	0
F6	168.2±5.49	PASS	150.9±6.87	120.33±5.78	2

*Sensation comfort score: 0 = very satisfied, 1 = quite satisfied, 2 = not satisfied, 3 = not at all satisfied.

Table 4. Pharmacokinetic parameters of different MS treatments administered to six rabbits

	Treatment 1 (F5 sublingual tablet)	Treatment2 (Kokast®)
Dose (mg)	5	5
T_{max} (hr)	1.5	4
C_{max} (µg/ml)	1.798	0.979
V_d(L)	2.214	2.861
AUC_{0-24} (µg.hr/ml)	8.873	5.666
$AUC_{0-\infty}$(µg.hr/ml)	9.455	6.107
RB %	**154.822**	---------

Table 5. One-Way Analysis of Variance (ANOVA) of MS formulae with respect to C_{max} and AUC_{0-24}after the bioavailability study

	C_{max}			AUC_{0-24}		
Source of Variation	Degrees of Freedom	Sum of Squares	Mean square	Degrees of Freedom	Sum of Squares	Mean square
Treatments (*between columns*)	2	2.157	1.079	2	32.084	16.042
Residuals (*within columns*)	15	0.5051	0.03367	15	4.23	0.282
Total	17	2.662		17	36.314	
F value	32.038			56.894		

Fig 1. IR Spectra of: A) MS. B) Mixture of MS and Crospovidone.C) Mixture of MS and Ac.Di.Sol.

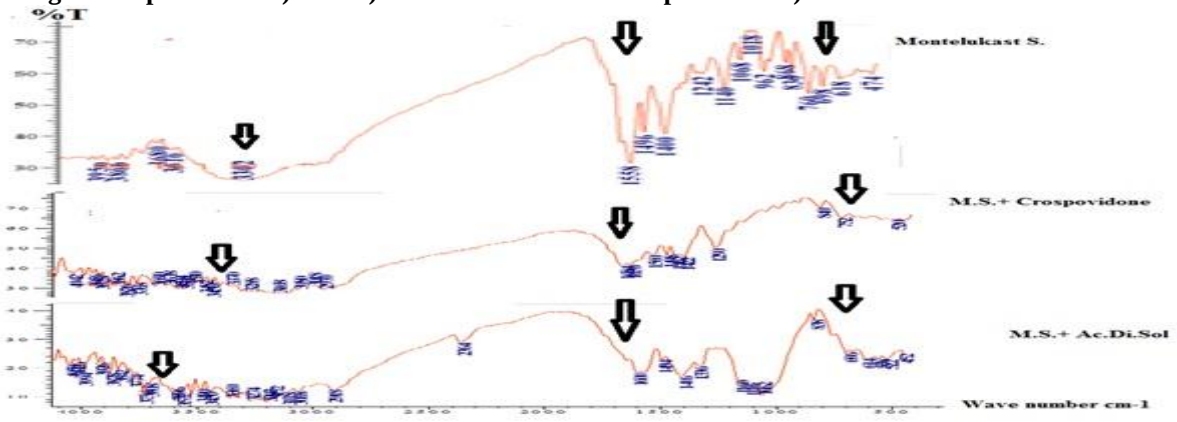

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Fig 2. DSC thermograms of: A) Montelukast Sodium. B) Mixture of MS and Crospovidone.C) Mixture of MS and Ac.Di.Sol.

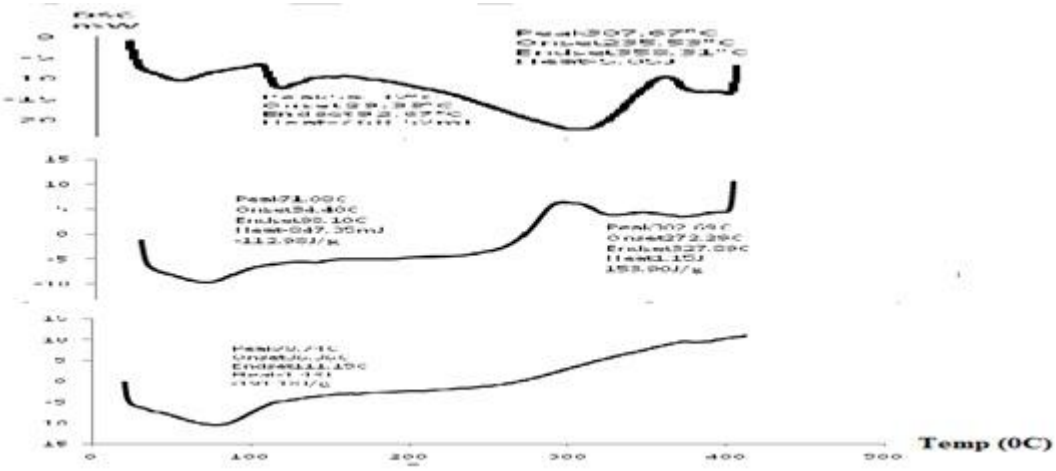


Fig 3. In- vitro dissolution profile of MS sublingual tablets prepared by direct compression technique.

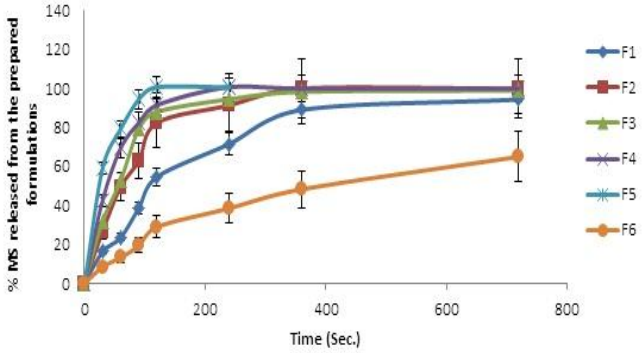
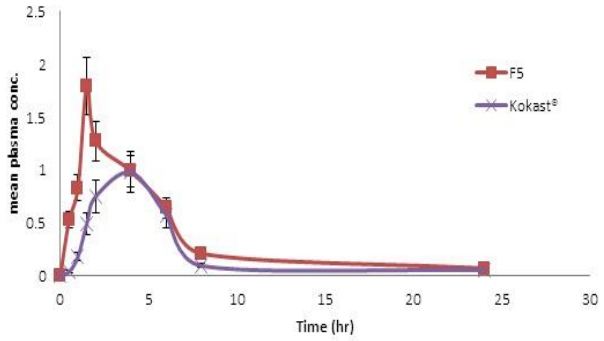
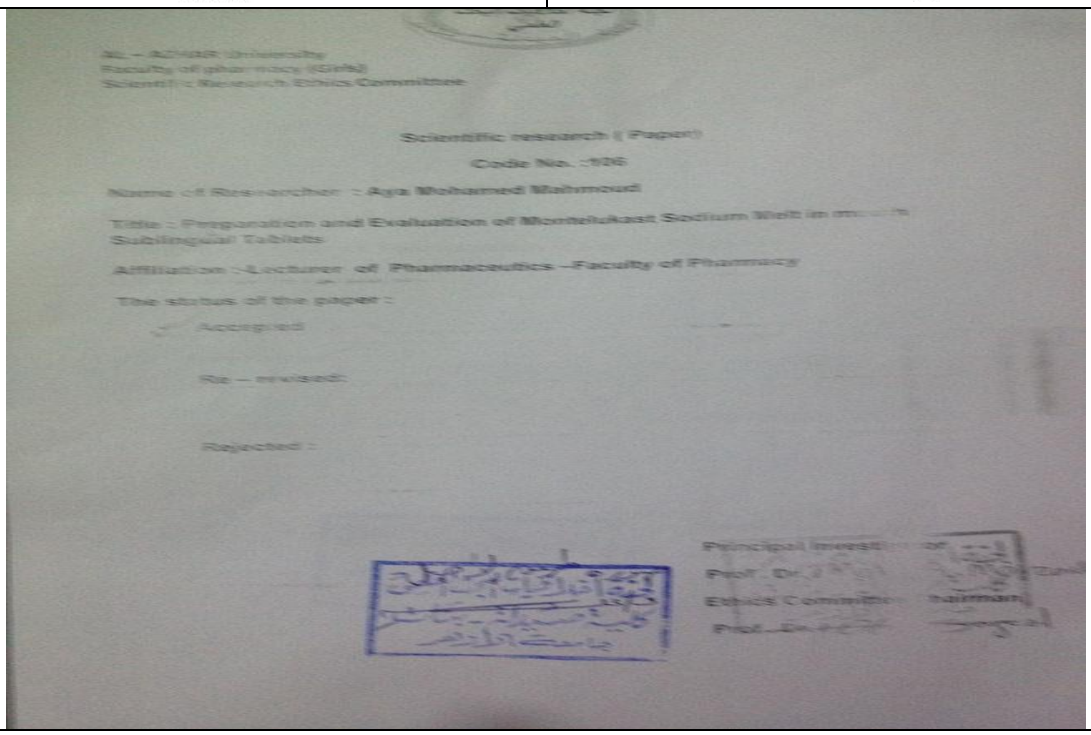


Fig 4. Mean plasma concentration of MS following sublingual administration of Kokast® and F5 to rabbits.





DISCUSSION

FT-IR spectroscopy

The IR spectrum of MS alone exhibits its major bands at 3302 cm^{-1} for O-H stretching band indicating overlapping of these peaks. The peaks due to the C-H structure of aryl group and C-H stretching of methyl group peaks have appeared as shoulders between 2900 cm^{-1} to 3100 cm^{-1}.The C=O peak has appeared at 1566 cm^{-1} along with a merged peak at 1558 cm^{-1}. The C-N stretching has appeared at 1140 cm^{-1} then C-Cl stretching has appeared at 760 cm^{-1}. It was clear that all characteristic bands of MS were appeared in the same regions and at the same ranges and there were no new bands appeared might be indicative of absence of interaction between MS and polymer or tablet's excipients used.

The DSC thermogram of MS is characterized by a characteristic sharp endothermic melting peak at 307.67°C with Peak onset 235.53°C and Peak end at358.31°C and heat of transition -672.69 J/g and small characteristic endothermic melting Peak at 119.55°C.The DSC thermogram of crospovidone and Ac-Di-Sol show endothermic peaks at 78.4°C and 77.42°C respectively. Polymers and MS peaks appear at the same positions. These results were matched with that of FTIR spectroscopy which indicates that the drug, the used polymers and tablet ingredients are compatible with each other

Preparation of MS sublingual tablets

The development of sublingual disintegrating tablets provides an opportunity to take into account the role of disintegrants. Recently, chemically modified disintegrants termed as superdisintegrants have been developed to improve the disintegration processes [(26).] Crospovidone is effective in improving the dissolution of the drugs in extra-granular mode of addition seems to be the best mode of incorporation, irrespective of the solubility of the main tablet component. Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration. Unlike other superdisintegrants which rely principally on swelling for disintegration, crospovidones uses a combination of swelling, wicking and deformation [27].

Evaluation of MS tablets

The weight variation values for all the formulae were found to be within the acceptable limits. All tablets that were produced passed the uniformity of weight test as all formulae had weight data with relative standard deviations of < 7.5%. Weight variations tests are very important consideration when formulating dosage forms as large variations in weight may be an indication of poor flow properties of powders [28] and will most likely result in the production of formulae of tablets that are not uniform with regards to API content, hardness test indicates good mechanical strength. The friability values of tablets belonging to all formulations complied with the limits set by the BP [29]. It is obvious that the drug content of all the investigated tablets complied with the pharmacopoeia specifications.

Post compression parameters

Wetting Time

It was observed that when crospovidone was used as disintegrant, the tablet wetting time is shorter for tablets containing high percentage of crospovidone, namely F5due to easy swelling ability of crospovidone when compared with other tablets and also may be due to lower porosity of Ac-Di-Sol [24, 31, 32].

Dispersion Test

By passing the test for dispersion, all of the prepared tablets are expected not to cause an unacceptable feeling of grittiness in the mouth as all the water insoluble diluents such as microcrystalline cellulose, dicalcium phosphate and HPC were omitted from the study. And also among the soluble diluents, Mannitol was selected as a model soluble diluent considering its advantages in terms of easy availability, cost-effectiveness, negative heat of dissolution and relative moisture insensitivity [24, 32].

In-vitro and In-vivo Disintegration Time

Indeed, the in-vivo disintegration time values were smaller than that of the in-vitro ones and this can be attributed to the fact of pressing effect of the tongue which enhance the disintegration time. The disintegration time of tablets in the mouth was reported to be related to the penetration rate of water into the tablets [(33).] Moreover, the subjects expressed a high degree of satisfaction only with the tablet formulations (F5 and F4) in terms of disintegration time, comfort sensation and taste (score 0). Also formulations (F6, F1, F2and F3) give an unpleasant disintegration time and tend to adhere to the sublingual mucosa so the subjects judged these tablets as unacceptable (score 2). Tablets of crospovidone: Ac-Di-Sol of 3:1 show excellent acceptability by the subjects because of its very short disintegration time (score 0), pleasant taste and comfort ability.

So, Formulae F5 was selected for further stability study due to further stability study due to its excellent physical profile characteristics, suitable weight and hardness values, least disintegration time and the highest dissolution rate.

Accelerated Stability Testing

After the six months storage period, the physiochemical properties of tablets like disintegration time and dissolution rate were found to be within the limits; which proved that MS sublingual tablet were stable at the end of the six months period.

Bioavailability study

Rabbits were selected as an animal model for absorption studies due to its convenient size, which allows for sublingual administration and blood sample volumes that are sufficient for quantitative analysis. In addition, rabbits have been described as one of the few laboratory animals that do not have keratinized mucosa, thus closely resembling human sublingual mucosal tissue [30]. Twelve healthy male albino rabbits weighing 2.5-3.5 kg were utilized for this study and divided into two groups (six animals for each group).Group (1): Using formula containing 5 mg of MS tablet F5.Group (2): Using commercial table containing 5 mg of MS (Kokast®) tablets. The study was a single dose, three –treatment parallel study. The rabbits were fasted overnight with free access to water. The blood samples (3 ml) were withdrawn via the marginal ear vein into heparinized tubes at specified time intervals 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hr post-dose of reference and prepared sublingual formula. The blood samples collected in heparinized tubes. Blood samples were then centrifuged at 3000 rpm for 10 min and the resulting plasma fraction was transferred by pipetting into pre-labeled polypropylene screw-cap tubes, followed by storing at −80°C until being assayed for MS content. The concentration of MS in rabbit's plasma samples was determined using the HPLC procedures reported [35].

Table5 shows the stastial analysis by using ANOVA reveals that regarding C_{max}, the P value is < 0.005, considered extremely significant. Variation among column means is significantly greater than expected by chance. Regarding$AUC_{0-24,}$ The P value is < 0.005, considered extremely significant. Variation among column means is significantly greater than expected by chance.

CONCLUSION

The present study conclusively indicates that formulation F5 (crospovidone: Ac-Di-Sol of 3:1) is very much promising as sublingual tablet of MS with excellent physical appearance, suitable weight and thickness values, least disintegration time, the highest dissolution rate, best relative bioavailability, highest $C_{max}$and $AUC_{0-\infty}$.

ABBREVIATIONS

API: Active pharmaceutical ingredient.
SD: Standard Deviation.
%RSD: Percent Relative Standard Deviation.
RB: Relative Bioavailability.

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DECLARATION OF INTEREST

The authors report no declarations of interest.

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