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Spectrophotometric determination of Montelukast Sodium in pure form and in its pharmaceutical formulations

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Abstract

A simple, sensitive and rapid spectrophotometric method for determination of Montelukast Sodium (MON) in both pure form and pharmaceutical formulations was developed. This method was based on the oxidation of the studied drug in presence of acidic medium by a known excess of (Potassium bromide: Potassium bromate) (KBr:KBrO3) and subsequent determination of unreacted oxidant by reacting it with Crystal Violet (CV) dye [4 [bis [4 (dimethylamino) phenyl] methylidene] cyclohexa-2,5-dien-1-ylidene]-dimethylazanium to produce blue product at λmax. 592 nm. The linearity range was found to be (5-50)µg/ml and molar absorptivity 1.5691×104 L/mol.cm, correlation coefficient 0.9993 and the limit of detection 0.209 µg/ml. This method was successfully applied for the determination of (MON) in tablet formulation.

التقدير الطيفي لمونتيليوكاست الصوديوم بشكله النقي وفي مستحضراته الصيدلانية

قبس ناجي رشيد عبد الهادي محمد نصيف

الخلاصة

تم استحداث طريقة بسيطة وحساسة وسريعة لتقدير المركب الدوائي مونتيليوكاست الصوديوم بشكله النقي وفي مستحضراته الصيدلانية. اعتمدت الطريقة على أكسدة (MON) في الوسط الحامضي باستخدام عامل مؤكسد (بروميد البوتاسيوم: برومات البوتاسيوم) (KBr:KBrO3) يليها اضافة صبغة البنفسج البلوري
[4- bis [4-(dimethylamino) phenyl]methylidene]cyclohexa-2,5- (CV) Crystal Violet
dien-1-ylidene]- dimethylazanium; chloride والتي تتفاعل مع المتبقي من العامل المؤكسد ليتكون ناتج أزرق والذي أعطى أعلى قيمة امتصاص عند طول موجي 592 نانومتر، ومدى الخطية كان عند التراكيز (5-50) مايكروغرام/مل، وبامتصاصية مولارية 1.5691×104 لتر/مول.سم ومعامل ارتباط 0.9993، وكان حد الكشف 0.209 مايكروغرام/مل، طبقت الطريقة بنجاح في تقدير (MON) في المستحضرات الصيدلانية على شكل أقراص.

الكلمات المفتاحية: مونتيليوكاست الصوديوم، (بروميد البوتاسيوم:برومات البوتاسيوم)، صبغة البنفسج البلوري، مطيافية.

Introduction

Montelukast Na (Fig.1), "used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies" [1,2], and used to prevent wheezing, difficulty breathing, chest tightness, and coughing caused by asthma. Montelukast is also used to prevent bronchospasm (breathing difficulties) during exercise. It is also used to treat the symptoms of seasonal (occurs only at certain times of the year), and perennial (occurs all year round) allergic rhinitis (a condition associated with sneezing and stuffy, runny or itchy nose). It is in a class of medications called leukotriene receptor antagonists (LTRAs). It works by blocking the action of substances in the body that cause the symptoms of asthma and allergic rhinitis [3]. Molar mass is 608.169 gm/mole, M.P. = 242.5 °C, is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile, chemically known is sodium; 2-[1-[[(1R)-1-[3-[(E)-2-(7-chloroquinolin-2-yl) ethenyl] phenyl] -3-[2-(2-hydroxypropan-2-yl)phenyl]propyl]sulfanylmethyl]cyclopropyl]acetate [4]. Several methods have been proposed for determination of this drug, such as HPLC [5-7], TLC [8,9], HPTLC [10-12], Voltammetry [13,14], UV-Vis. Spectrophotometry [15-18].

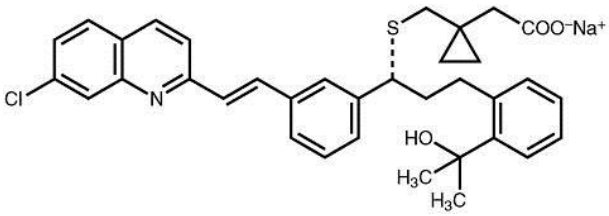


Fig. (1): Chemical Structures of Montelukast Na

The research aims to develop a simple, fast and economical spectrophotometric methods for determination of Montelukast Na by using dye with an oxidizing agent in the acid medium.

Experimental

Apparatus

T90 UV-VIS spectrophotometer double beam (PG Instruments Ltd, with 1 cm quartz cells), UV-VIS spectrophotometer single beam (Genesys UV 10), pH meter InoLab

pH/INO735 (Jenway 3310), Balance Kern 770GS/GJ (Sartorius BL210S), Oven (Memmert, Schutzart DIN 40050-IP20).

Materials

Monteiukast Na %99 (SDI Samarra-Iraq), KBr %99 (Merck), $KBrO_3$ %98 (Fluka), Crystal Violet (dye) %90 (Fluka), Ethanol %99.9 (Scharlau), H_2SO_4 %98 (GCC), HCl %36 (Thomas baker), HNO_3 %70 (GCC), CH_3COOH %98 (Scharlau), Lactose %99.5 (BDH), Mannitol %97 (Merck), Sodium benzoate %99 (BDH).

Solutions

Montelukast Na Stock solution (1000 µg/mL): An exactly (0.1000 gm) of (MON) "standard" were dissolved in (100 ml) ethanol.

(KBr: $KBrO_3$): prepared by dissolving 1.0gm of potassium bromide, and 0.1000gm of potassium bromate in 100 ml distilled water [19], then 2.5 ml of this mixure were diluted to 100 ml distilled water in a volumetric flask.

Crystal Violet (CV) dye: a concentration of $7.7x10^{-5}$ M was prepared by dissolving 0.0031 gm in 100 ml distilled water.

Sulfuric acid solution: an approximate concentration of 1.0 molar was prepared by diluting 5.4 ml of concentrated acid (18.4 M) to 100 ml distilled water.

Hydrochloric acid solution: an approximate concentration of 1.0 molar was prepared by diluting 8.6 ml of concentrated acid (11.64 M) to 100 ml distilled water.

Nitric acid solution: approximate concentration of 1.0 molar was prepared by diluting 6.3 ml of concentrated acid (15.78 M) to 100 ml distilled water.

Acetic acid solution: an approximate concentration of 1.0 molar was prepared by diluting 5.8 ml of concentrated acid (17.33 M) to 100 ml distilled water.

(Lactose, Mannitol and Sodium benzoate) solutions: a concentration of (1000 µg/mL) was prepared by dissolving (0.1000) gm in 100 ml distilled water.

Procedures

After initial testing, optimal conditions were obtained, and the procedure involves transferring 0.5 ml of 500 µg/ml (MON) to a 10 ml volumetric flask, then adding 0.75 ml of the oxidizing agent (KBr: KBrO3) by diluting (2.5 to 100 ml), followed by adding 0.5 ml of 1.0 M HCl acid. After 15 minutes, 1.0 ml of Crystal Violet dye were added, and after 5 minutes, the volume is completed with ethanol to 10 ml, because after five minutes the color of the blank disappears, the highest absorption of the resulting compound (blue color) absorbs at 592 nm.

Procedures for "stoichiometric ratio"

The reaction of equivalence between this drug and the reagent (dye), have been estimated by carrying out "molar ratio" and "continuous variation method". In these methods, "equimolar" solutions of (MON 0.5 ml) and "CV dye" (7.7×10^{-5}M) were used. In the first method varying aliquots of "CV dye" was added to constant aliquots of drug solution, final volumes (10ml) and the absorbance was measured at 592 nm, opposite the blank treated similarly. while in the latter method, a series of MON:CV dye solutions was kept at (5ml) (0**:**5, 0.5**:**4.5, 1**:**4, 1.5**:**3.5, 2**:**3, …… 5**:**0).

Application of the proposed methods

Ten tablets (2.465gm, 1.859gm and 2.040gm) respectively, from each preparation, were grinded into fine powder. An precisely weighed amount of powder was transferred into a beaker and then were shaken with 50 ml of solvent (ethanol) and filtered. The filtrates and the washings were collected in a 100ml volumetric flask. and diluted up to the mark with solvent to obtain final concentration of 1000 µg/mL. The suggested method was successfully applied for the determination of MON in various

commercial tablets; the results are shown in Table (4).

Results and Discussion

Absorption spectrum of blue color product of MON against the blank at room temperature (25^{o}C) at 592nm is shown in (Fig. 2), and the blank against distilled water is shown in (Fig. 3).

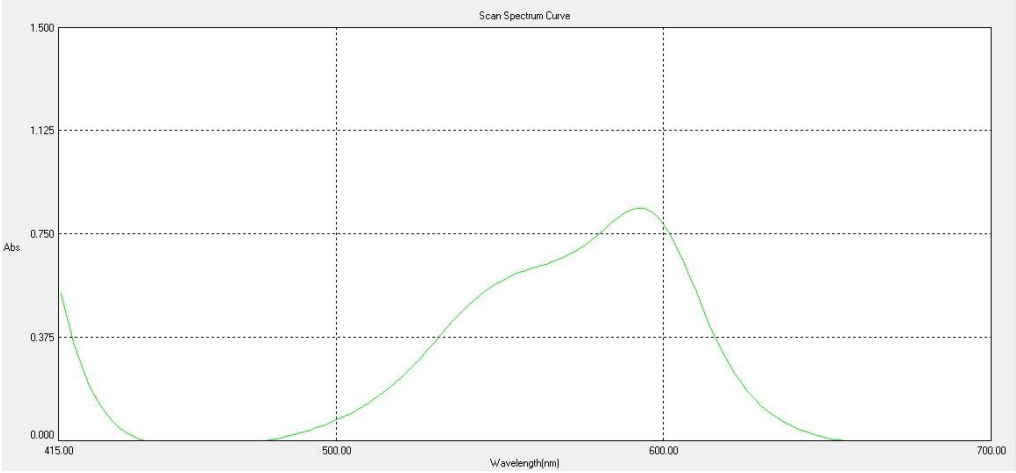


Fig. (2):- Absorption spectrum of "color product of MON"system against blank

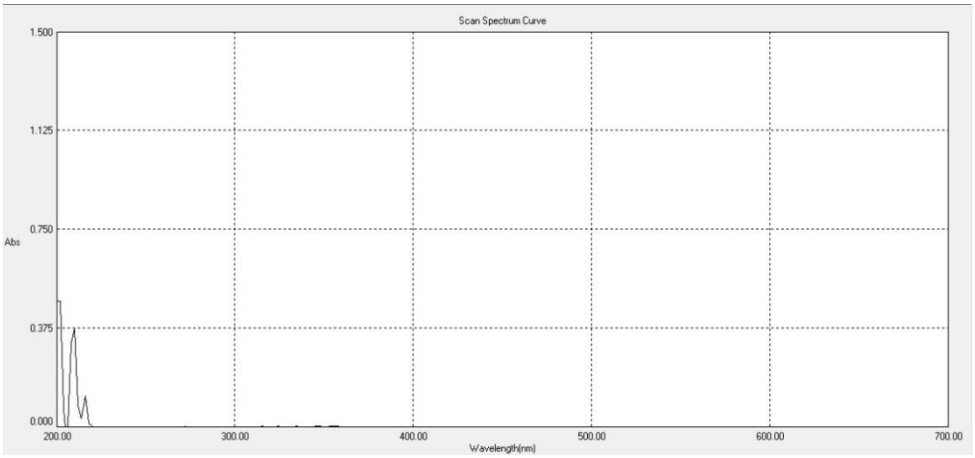


Fig. (3):- Absorption spectrum of the blank against distilled water

Optimum conditions

Effect of oxidation agent volume

Different and increasing volumes of oxidizing agent mixture (KBr: $KBrO_3$) were added to Know their effect on the absorption of the resulting product, It is clear from Fig. (4) that the best volume of the oxidizing agent is 0.75 ml which was used in subsequent studies.

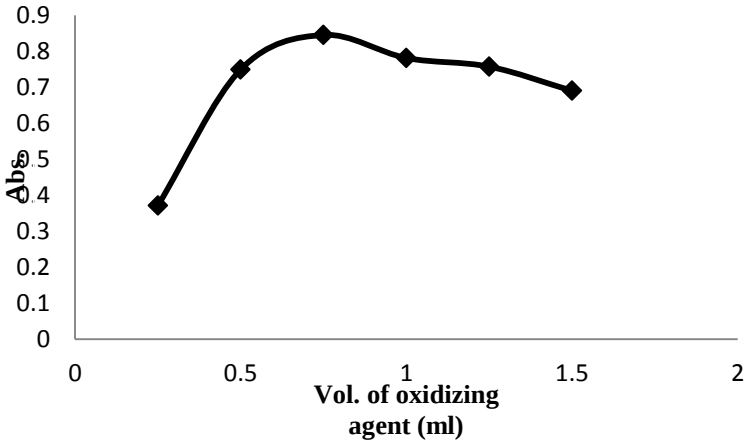


Fig. (4):- Effect of oxidizing agent volume (KBr: $KBrO_3$) on absorption of the (MON) product

Effect of the use of different acids

The acids used were (H_2SO_4, HCl, HNO_3, CH_3COOH), with a concentration of 1.0 M for each, and same volume of 0.5 ml for each, Table (1) shows that the best acid used to form the product is hydrochloric acid.

Table (1):- Effect of different types of acids on absorption values of the product

The acid used	Product absorption values
HCl	0.845
H_2SO_4	0.595
HNO_3	0.478
CH_3COOH	0.0

Effect of the acid amount

Different volumes (0.2-2)ml of 0.1 M HCl were used, As shown in Fig. (5), the optimal added acid volume is 0.5 ml, after which, the color of the formed product disappears gradually.

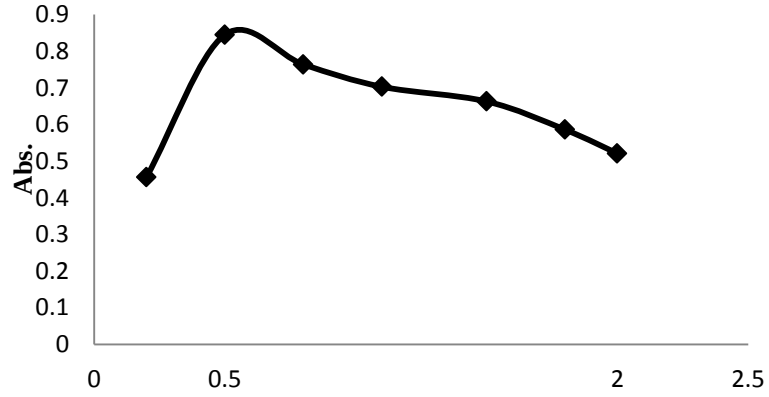


Fig. (5):- Effect of HCl on the absorption values of the product

Effect of the dye amount

Fig. (6) shows the effect of adding different volumes (0.5-3) ml of the CV dye on the absorption of the product. The best added volume was 1.0 ml.

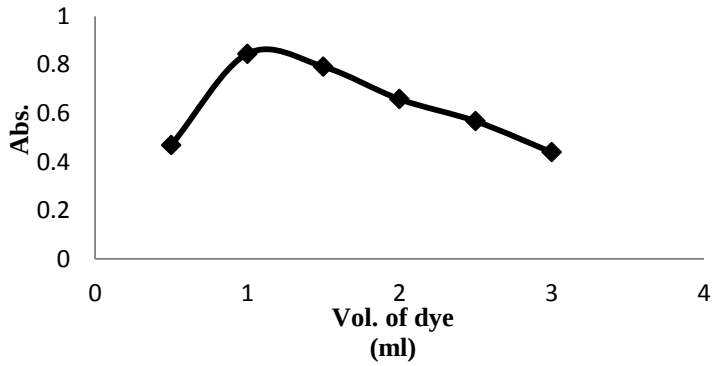


Fig. (6):- Effect of CV dye volumes on product absorption values

Effect of time on product stability

The effect of time was followed using optimum conditions every ten minutes for three hours, the product absorption was then taken the next day. Table (2) shows the stability of the absorption values at λmax. with time, the absorption value of the product is fixed for 24 hours.

Table (2):- Effect of time on Stability of product

Time (min.)	Absorbance
5.0	0.792
10	0.845
20	0.844
30	0.845
40	0.843
50	0.843
60	0.844
120	0.845
180	0.844
24 hours	0.840

Effect of Interferences

The effect of interferences on the composition of the product was studied, and not observed any effect, as shown in the table (3).

Table (3):- Effect of interferences

Interference	Added con. µg/mL	% RE	Added con. µg/mL	% RE
Lactose	50	-1.657	100	-2.13
Manitol	50	-3.787	100	-4.497
Sodium benzoate	50	-0.71	100	-1.657

The stoichiometry of the product

Under the optimum conditions, the stoichiometry of the reaction between MON and the dye was studied by mole–ratio and continuous variation methods. The equivalence between dye and this drug was 1:1 (Figs. 7, 8).

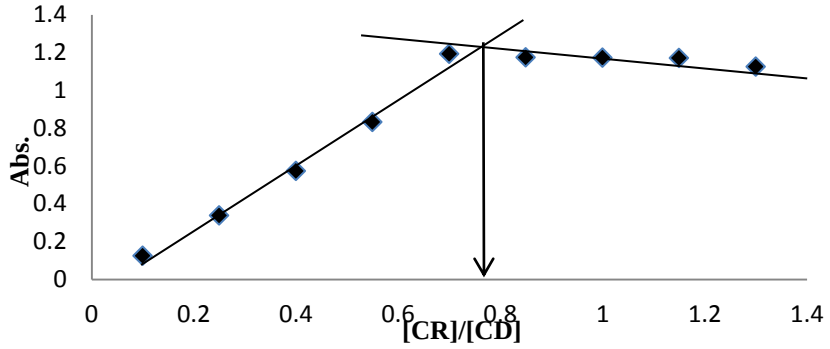


Fig.(7):- Mole-ratio method of MON product

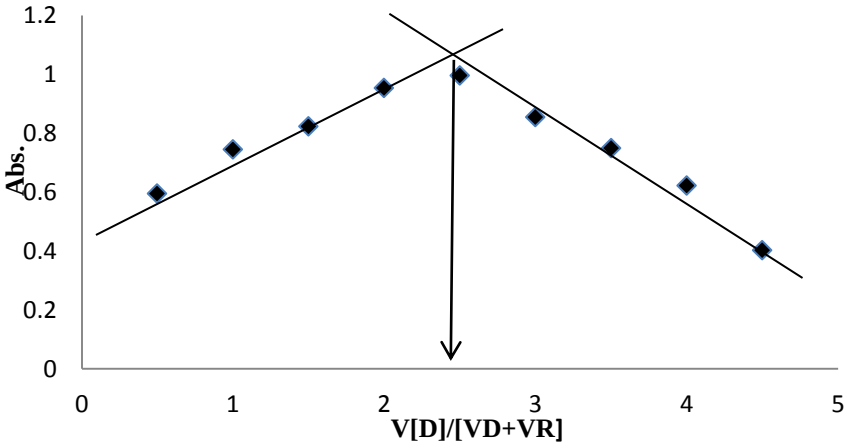


Fig.(8):- Continuous variation method of MON product

Calibration curve

Fig.(9) shows the linearity of the calibration curve obtained at optimal conditions, where the linearity was within concentrations (5-50) µg/ml, which is equal to the volumes within (0.1-1.0) ml.

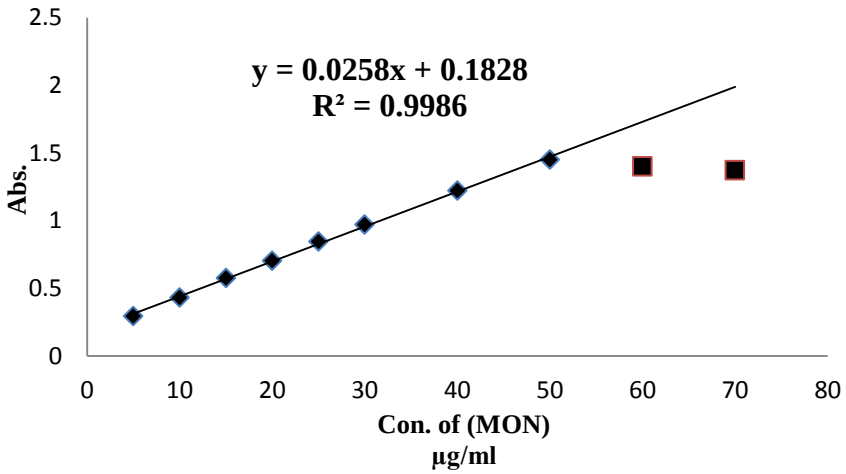


Fig. (9):- Calibration curve of MON product

Characteristics of calibration curve

Calibration curve was constructed according to the optimum conditions in table (4).

Table (4):- characteristics of the calibration curve for spectrophotometric determination of MON

Parameter	Value
λ_{max}.(nm)	592
Beer's law (µg/ml)	5-50
Molar absorptivity(L/mol.cm)	1.5691×10^{4}
Correlation coefficient (r)	0.9993
Limit of Detection (µg/ml)	0.209
Slope	0.0258
Intercept	0.1828
%RSD	0.174

Application of the proposed methods

The results of determination of MON in the pharmaceutical preparations are shown in table (5).

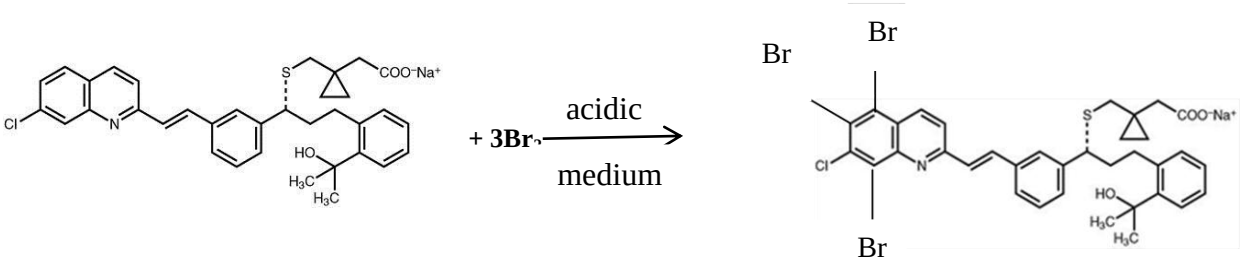
Table (4): Determination of MON in commercial tablets by the proposed spectrophotometric method

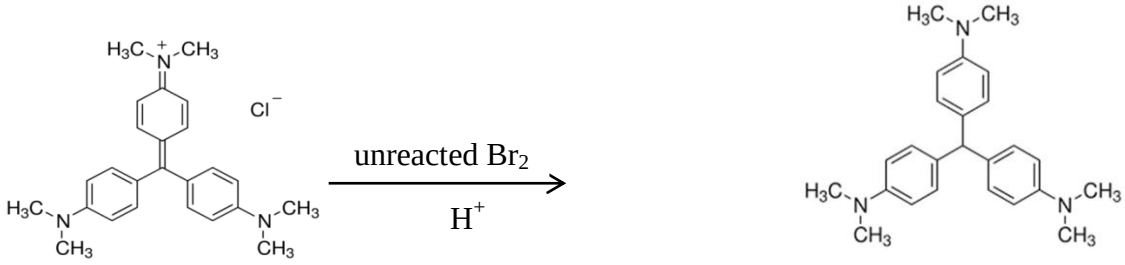
pharmaceutical preparations	Content(mg) declared	Found(mg) by proposed method	%RE	%Recovery
Montix (Pioneer)	10	10.04	0.4	100.4
	10	9.93	-0.7	99.3
	10	10.12	1.2	101.2
Lukast (Pharma International)	10	9.99	-0.1	99.9
	10	9.82	-1.8	98.2
	10	10.23	2.3	102.3
Singular	10	10.22	2.2	102.2
	10	10.02	0.2	100.2
	10	9.69	-3.1	96.9

The suggested ractions

The proposed reaction can be based on how the MON drug is oxidized, by connection three groups of bromine to the ring connected by the halogen group [20], and how to convert the CV dye to Leuco form[21] as follows:

$$BrO_3^- + 5Br^- + 6H^+ \longrightarrow 3Br_2 + 3H_2O$$





(CV) dye

Leuco form

Conclusion

This method described here is simple, rapid, convenient and do not requires special working conditions unlike many other reported methods. The procedure showed shorter reaction time, stable colored species with inexpensive reagent. The determination can be performed at room temperature and do not require heating step. The proposed method can be applied for the determination of MON in pharmaceutical preparations (Tablet).

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