Journal of Pharma Creations (JPC)

JPC |Vol.11 | Issue 2 | Apr - Jun -2024

www.pharmacreations.com

DOI : https://doi.org/10.61096/jpc.v11.iss2.2024.123-130

ISSN: 2348-6295

Research

Formulation Development And Invitro Evaluations Of Zafirlukast Pulsatile Tablets

Arjun.Goje, Rubesh.S, Sunitha, Shabaaz.Syed, Thirupathi.V, Vamshi.J, Zehra.T.Syeda

Department of pharmaceutics, Teegala Ram Reddy College of Pharmacy, Telangana, India

* Address for Correspondence: Arjun.Goje
Email: Teegalaramreddymailbox@gmail.com

Published on: 18 May 2024

Published by:
DrSriram Publications

Abstract

From the above experimental results it can be concluded that, Formulated tablets gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity. HPMC and Ethyl cellulose has predominant effect on the lag time, while also shows significant effect on drug release. Zafirlukast Press coated tablet shows a delayed release pattern. Among all the core tablet formulation F8 was selected based on drug release within a given period of time. In-vitro release rate studies showed that the maximum drug release was observed in P3F8 formulations was optimized based on less amount of drug release during lag time. FT-IR studies revealed that there was no interaction between Zafirlukast and the polymers.

Keywords: Zafirlukast, Controlled drug delivery system, Press- coated tablets

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R &D sector. Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as pulsatile release.[1]

ThePulsincap® system consists of a water-insoluble capsule body (exposing the body to formaldehyde vapor which may be produced by the addition of trioxymethylene tablets or potassium permanganate to formalin or any other method), filled with the drug formulation and plugged with a swellable hydrogel at the open end[2]. Upon contact with dissolution media or gastrointestinal fluid, the plug swells and comes out of the capsule after a lag time, followed by a rapid release of the contents[3,4]. The lag time prior to the drug release can be controlled by the dimension and the position of the drug. In order to assure a rapid release of the drug content, effervescent agents or disintegrants were added to the drug formulation, especially with water-insoluble drug. Studies in animals and healthy volunteers proved the tolerability of the formulation (e.g., absence ofgastrointestinal irritation)[5]. In

order to overcome the potential problem of variable gastric residence time of a single unit dosage forms, the Pulsincap® system was coated with an enteric layer, which dissolved upon reaching the higher pH regions of the small intestine[6].

Delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms, because conventional systems with acontinuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release[7,8].

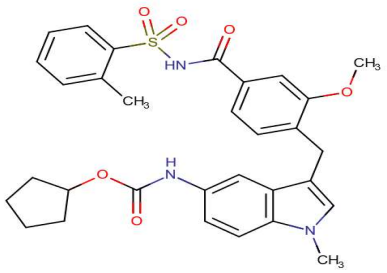
These dosage forms offer many advantages such as

- ✓ Nearly constant drug levels at the site of action.
- ✓ Avoidance of undesirable side effects.
- ✓ Reduced dose and
- ✓ Improved patient compliance.
- ✓ Used for drugs with chronopharmacological behaviour, a high first pass effect the requirement.

Drug profile

Name:Zafirlukast

Structure: Zafirlukast



Brand names: Accolate

Weight: Average: 575.675

Monoisotopic: 575.209006493

Chemical Formula; $C_{31}H_{33}N_3O_6S$

IUPAC Name: cyclopentyl N-[3-({2-methoxy-4-[(2-methyl benzene sulfonyl) carbamoyl] phenyl} methyl)-1-methyl-1H-indol-5-yl]carbamate

MATERIALS AND METHODS

Materials used

Table 1: The Materials used in the present work are as follows.

S NO	Materials	Name of the supplier
1	Zafirlukast	Chandra labs, hyd
2	Cross povidone	MYL CHEM Mumbai
3	Sodium starch glycolate	MYL CHEM Mumbai
4	Magnesium stearate	S.D Fine chem. LTD Mumbai
5	Micro crystalline cellulose	S.D Fine chem. LTD Mumbai
6	Cross caramellose sodium	MYL CHEM Mumbai
7	HPMC	S.D Fine chem. LTD Mumbai

Equipments used

Table 2: The equipments used in the present work are as follows

S.No	Instruments	Source
1	Electronic balance	Shimadzu
2	UV/Visible Spectrophotometer	Corporation-BL-220H
3	FTIR spectrophotometer	Corporation japan
4	Magnetic stirrer	Remi motor equipments

5	Dissolution apparatus	Shimadzu
6	Oven	Biotech india.
7	pH meter	Shital scientific industries
8	Compression machine	Cadmach machinery

METHODOLOGY

Preformulation studies[17]
Organoleptic evaluation

a) Color
b) Odour
c) Taste

Analytical methods for the estimation of zafirlukast[36]
Determination of λ max for Zafirlukast

On the basis of preliminary identification test, it was concluded that the drug complied the preliminary identification. From the scanning of drug, it was concluded that the drug had λ max of 242 nm.

Preparation of standard calibration curve of Zafirlukast

The standard calibration curve for Zafirlukast was prepared using 0.2 % of SLS.

Standard solution:

10 mg of Zafirlukastwas dissolved in few ml of methanol and make up with 0.2 % of SLS to give a concentration of 1 mg/ ml (1000 µg/ml).

Stock solution

From standard solution take 10 ml of solution in 100 ml of solution to produce the 100 µg/ml concentration and take from the 100 µg/ml of the solution. Aliquots of 0.5, 1, 1.5, 2, 2.5 ml of stock solution were pipette out in 10 ml volumetric flask. The volume was made up to mark with SLS solution to produce concentration as 5, 10, 15, 20, and 25 µg/ml of Zafirlukast respectively.

The absorbance of prepared solution of Zafirlukast was measured at 242 nm in Shimadzu UV/visible 1700 spectrophotometer against 0.2 % of SLS solution as blank. The absorbance data for standard calibration curve are given in Table and plotted graphically as shown in the Figure. The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 5 to 25 mcg/ml.

Drug – Excipient Compatibility Study

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of solid fine powder of drug and 200-300 mg of dry powder of KBr(IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm^{-1} by FTIR spectrophotometer

Formulation development[9,10]
Formulation of core tablets by direct compression:

- The inner core tablets were prepared by using direct compression method.
- As shown in Table powder mixtures of Zafirlukast, microcrystalline cellulose , cross-carmellose sodium (Ac-Di-Sol) ,SSG, crospovidone ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate.
- The mixtures were then further blended for 10 min., 200mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with 8mm punch and die to obtain the core tablet.

Table 3: Composition of core tablets

Ingredients	F 1	F2	F 3	F 4	F5	F6	F7	F8	F9
Zafirlukast	10	10	10	10	10	10	10	10	10
HPC	10mg	-	-	20mg	-	-	25mg		-
CCS	-	10mg	-	-	20mg	-	-	25mg	-
SSG	-	-	10mg	-	-	20mg	-	-	25mg
Magnesium stearate	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg

MCC	176mg	176mg	176mg	166mg	166mg	166mg	161mg	161mg	161mg
Total wt	200	200	200	200	200	200	200	200	200

MCC: Micro crystalline cellulose, CCS: Cross caramellose sodium, SSG: Sodium starch glycolate

Preparation of press-coated tablets[9]

The core tablets were press-coated with 300mg of mixed blend as given in Table. 150mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the centre. The remaining 150mg of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

Table4: Composition of Zafirlukast press-coated Tablets

Press coat	P1 F8 (mg)	P2 F8 (mg)	P3 F8 (mg)	P4 F8 (mg)
HPMC	150	100	--	300
Ethyl cellulose	150	200	300	--
Total wt(mg)	500	500	500	500

RESULTS AND DISCUSSIONS

Pre-formulation studies

Description

Table 5: Table showing the description of Zafirlukast (API)

Test	Description
Colour	white to pale yellow amorphous powder
Odour	Free of odour

Solubility

Table 6: Table showing the Solubility of zafirlukast (API) in various solvents.

Solvents	Solubility
Water	practically insoluble
dimethylsulfoxide	Soluble
acetone	Soluble
Methanol	slightly soluble

Melting Point

Table 7: Table showing the melting point of API's

Material	Melting Point
zafirlukast	139 °C

Standard Calibration Curve For Zafirlukast

Table 8: Calibration Curve Data of Zafirlukastin 0.2% SLS

S.No	Concentration	Absorbance
1	0	0
2	5	0.230
3	10	0.366
4	15	0.570
5	20	0.727
6	25	0.908

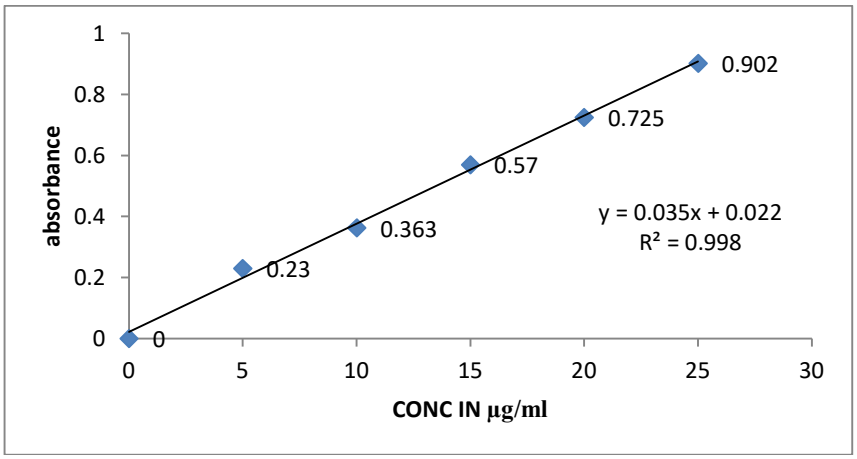


Fig 1: Clibration curve of zafirlukastin 0.2% SLS

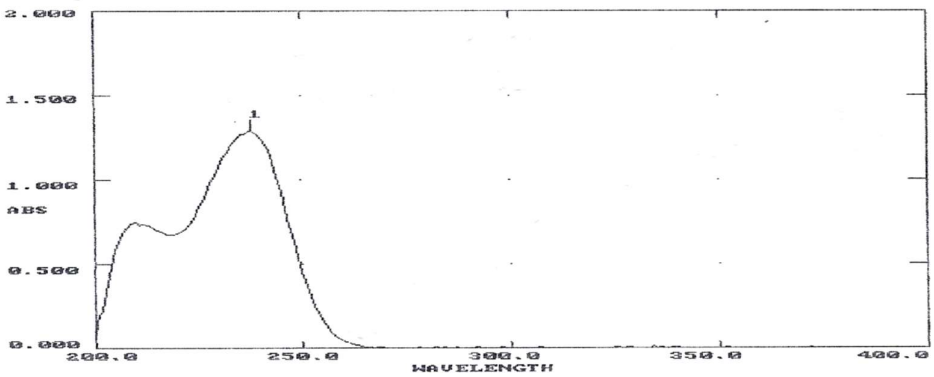


Fig 2: UV Spectrum for zafirlukast at 242nm

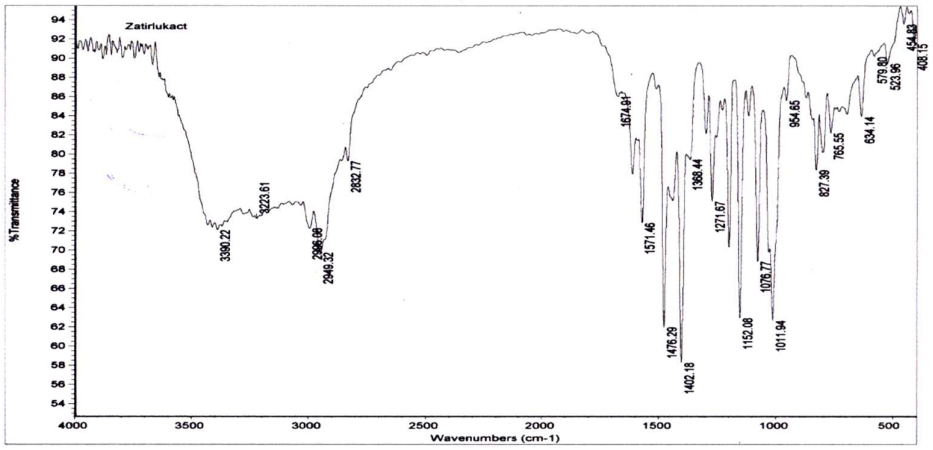


Fig 3: FTIR Spectra of Zafirlukast pure drug

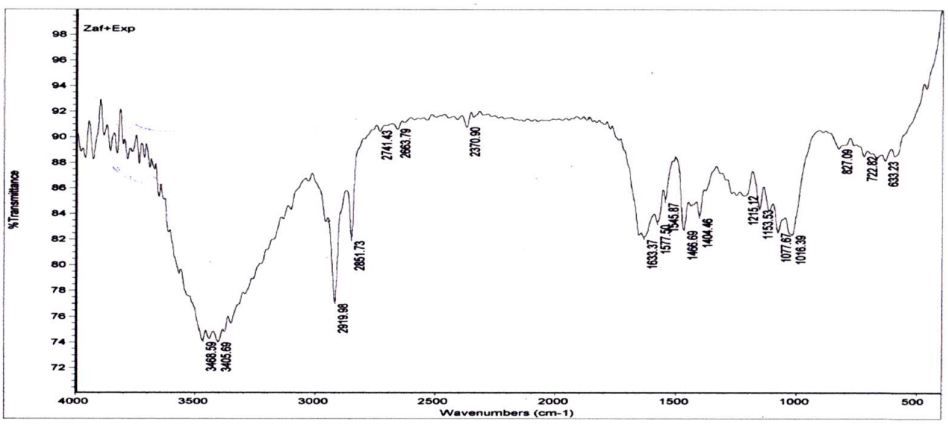


Fig 4: FTIR Spectra of Zafirlukast final formulation

Evaluation Parameters For Core Tablets

Table 9: Physical Evaluation Parameters for Core Tablets

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	**Weight variation**	199	201	199	198	202	200	200	198	201
2	**Hardness(Kg/cm^2)**	4.21	4.23	4.21	4.24	4.20	4.23	4.20	4.22	4.22
3	**Thickness(mm)**	3.34	3.32	3.34	3.31	3.35	3.30	3.31	3.32	3.35
4	**Friability %**	0.36	0.35	0.31	0.36	0.36	0.36	0.37	0.36	0.34
5	**Disintegration time**	2 min	1min 25 sec	1min	1min30sec	40sec	30sec	45 sec	1min	1min20 sec

Dissolution For Core Tablets

Table 10: Dissolution For Core Tablets

Dissolution time(Min)	Core formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	11.4	23.4	34.6	34.2	25.1	25.8	33.9	39.7	35.3
10	35.0	33.1	46.4	47.3	49.5	49.2	44.1	54.25	44.2
15	49.2	44.9	52.9	56.6	76.2	73.8	65.6	80.01	75.7
30	74.1	69.1	76.4	79.3	83.5	82.6	83.6	99.6	84.2
45	80.5	82.7	82.3	97.7	97.3	95.7	98.1	--	94.6
60	95.3	96.5	95.1	--	--	--	--	--	--

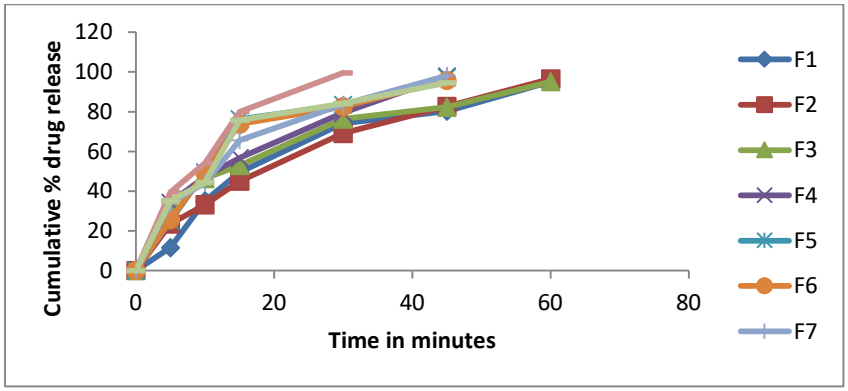


Fig 5: Dissolution graph for core formulations F1-F9

Based on the drug release within the required time period F8 was optimized and further formulated for Zafirlukast press-coated tablets.

Table 11: Evaluation Parameters for Zafirlukast press-coated Tablets

S. No	Physical parameter	P1F8	P2F8	P3F8	P4F6
1	**Weight variation**	501	500	499	498
2	**Hardness(Kg/cm^2)**	6.4	6.6	6.4	6.5
3	**Thickness(mm)**	4.3	4.4	4.3	4.4
4	**Friability %**	0.21	0.19	0.18	0.18

Dissolution Data For Press-Coated Tablets

Table 12: Dissolution data for press-coated tablets

Time in hrs	Press coat Formulation code			
	P1F8	P2F8	P3F8	P4F8
1	2.89	1.62	0	8.94
2	15.45	18.74	0	15.65
3	40.32	45.98	2.4	42.97
4	51.21	56.12	6.4	60.43
5	74.22	78.66	8.8	82.80
6	98.1	89.90	12.3	95.63
7	-	95.54	85.63	--
8	-	--	99.66	--

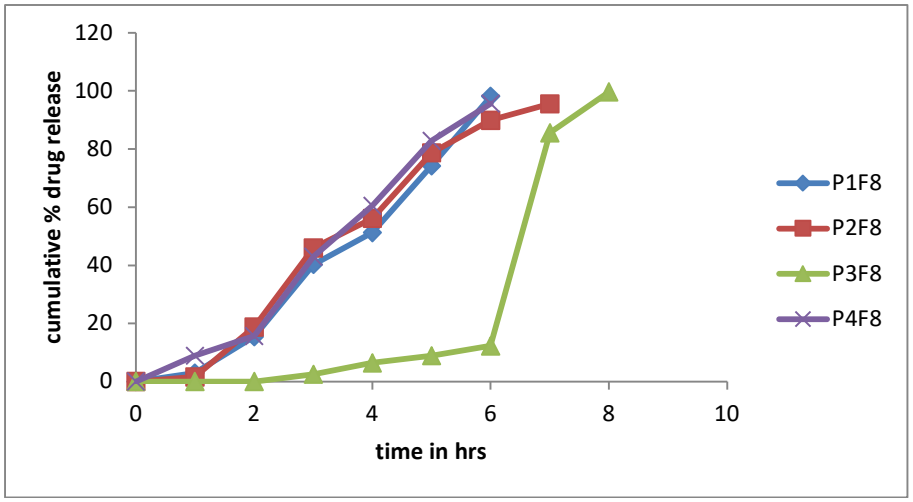


Fig 6: Dissolution graph for press-coated tablet of formulation

From the above core formulations F8 was selected for press-coated by using different synthetic polymers (HPMC and EC) in different ratios among which P3F8 was optimized based on the lag time 6 hours and percent of drug release and also further evaluated.

Stability Studies

Table 13: Stability Studies

	Cumulative % drug release during 6h		
Sampling interval	**25^{0}C/60%RH**	**30^{0}C/65%RH**	**40^{0}C/75%RH**
0 Days	98.9	98.9	98.9
30Days	98.0	98.1	98.1
60 Days	97.2	97.5	97.8

90 Days	96.8	96.8	96.8

CONCLUSION AND SUMMARY

From the above experimental results it can be concluded that, Formulated tablets gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity. HPMC and Ethyl cellulose has predominant effect on the lag time, while also shows significant effect on drug release.

- Zafirlukast Press coated tablet shows a delayed release pattern.
- Among all the core tablet formulation F8 was selected based on drug release within agiven period of time.
- In-vitro release rate studies showed that the maximum drug release wasobserved in P3F8 formulations was optimized based on less amount of drug release during lag time.
- FT-IR studies revealed that there was no interaction between Zafirlukast and the polymers.

REFERENCES

1. Gothaskar, AV, Joshi AM, Joshi, NH, 2004. Pulsatile drug delivery system a review. Drug Del. Technol. 4, http://www.drugdeliverytech.com/id article=250.
2. Shivkumar HG, Promod KTM, Kashappa GD. Pulsatile drug delivery systems .Indian JPharmaEdu 2003 July-Sep : 37(3) : 125:8.
3. Sarasija S, Stutie P. Chronotherapeutics: Emerging role of biorhythms in optimizing drug therapy. Indian J Phrm Sci. 2005 Mar;67(2):135-40.https://www.ijpsonline.com/articles/chronotherapeutics--emerging-role-of-biorhythms-in-optimizing-drug-therapy.pdf
4. Ross AC, Macrae RJ, Walther M, Stevens HN. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. Journal of pharmacy and pharmacology. 2000 Aug;52(8):903-9.https://academic.oup.com/jpp/article-abstract/52/8/903/6157620
5. Mastiholimath VS, Dandagi PM, Jain SS, Gadad AP, Kulkarni AR. Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma. International journal of pharmaceutics. 2007 Jan 2;328(1):49-56.https://www.sciencedirect.com/science/article/pii/S0378517306006375
6. Abraham S, Srinath MS. Development of modified pulsincap drug delivery system of metronidazole for drug targeting. Indian J Pharm Sci.2007; 69(1):18-23.Doi: 10.4103/0250-474X.32102
7. Samantha MK, et al. Designed and evaluated Pulsincap drug delivery system of Salbutamol sulphate for drug targeting to colon in disease condition like asthma. Ind. J Pharmcl Sci. 2000; 62(2): 102-107. https://www.ijpsonline.com/articles/development-of-pulsincap-drug-delivery-of-salbutamol-sulphate-for-drug-targeting.pdf
8. Jeong YI, Ohno T, Hu Z, Yoshikawa Y, Shibata N, Nagata S, Takada K. Evaluation of an intestinal pressure-controlled colon delivery capsules prepared by a dipping method. J Control Release. 2001 Apr 2;71(2):175-82. doi: 10.1016/s0168-3659(01)00211-5. PMID: 11274749.
9. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J Control Release. 2001 May 18;73(1):103-10. doi: 10.1016/s0168-3659(01)00291-7. PMID: 11337063.
10. Stevens HN, Wilson CG, Welling PG, Bakhshaee M, Binns JS, Perkins AC, Frier M, Blackshaw EP, Frame MW, Nichols DJ, Humphrey MJ, Wicks SR. Evaluation of Pulsincap to provide regional delivery of dofetilide to the human GI tract. Int J Pharm. 2002 Apr 2;236(1-2):27-34. doi: 10.1016/s0378-5173(02)00012-1. PMID: 11891067.