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Full Length Research Paper

Components analysis of volatile matter in simethicone by gas chromatography-mass spectrometry

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The aims of the present study were to analyze the chemical compositions of volatile matter in simethicone crude drug qualitatively and quantitatively. Gas chromatography-mass spectrum (GC-MS) method was used for the separation and determination of the volatile matter in simethicone. The qualitative analysis of volatile matter components in simethicone with the viscosity of 500-centistokes (cs) was studied by GC-MS, through the interpretation of the mass spectrogram and investigation of the law of peaks. Area normalization method was used for preliminary quantitative analysis according to the GC spectrogram. The total content of volatile matter in simethicone was determined by loss on heating method. 42 components in the sample were identified in our study, which accounted for 99.21% of the total volatile matter content, including two sets of homologous compounds: 20 species of linear methylpolysiloxane (MD_mM, MM to $MD_{21}M$) and 22 species of cyclic methylpolysiloxane (D_n, D_3 to D_{24}). Our study offered scientific evidence for improving the production condition and controlling the quality of simethicone.

Key words: Simethicone, volatile matter, gas chromatography-mass spectrometry (GC-MS).

INTRODUCTION

Simethicone is a mixture of polydimethylsiloxane (PDMS) and silicon dioxide, with lower surface tension, better biological and chemical stability (Yang et al., 2007; Ljerka et al., 1994). Simethicone is mainly used for treating gastrointestinal complaints caused by gas accumulation in the abdomen in clinical, such as belching, flatulence, and postoperative abdominal distention (Ruan, 2007; Lu and Li, 2008). It also can be used for treating functional dyspepsia (Lecuye et al., 2009), irritable bowel syndrome (Zhong et al., 2009; Li and Chang, 2006; Zhuang et al., 1999), postoperative ileus, and adjuvant of abdominal imaging examinations (for example, X-ray, ultrasonography, and gastroscopy). It is also reported that simethicone is used as an adjunct to contrast media suspensions (Sun et al., 2009; Wu et al., 2006).

The volatile matter in simethicone is from one of its components, PDMS, which is synthetized by hydrolysis and polycondensation of octamethylcyclotetrasiloxane (D_4) and hexamethyldisiloxane (MM) by using catalyst under certain temperature (Zhao, 2007). Although, PDMS was purified and refined after being synthesized, it still contains a small amount of low-molecular-weight components (LMWC, M <2400 doc). It is possible that the LMWC contains unreacted synthesis raw materials, broken chain by-products, low molecular weight PDMS components, or volatile impurities. Previous studies have shown that the LMWC in simethicone may cause silicone oil emulsion (Heidenkummer et al., 1991, 1992; Nakamura et al., 1991; Garrido et al., 1993), which was related to the adverse effects of the silicone oils in eye, such as glaucoma and keratitis (Han et al., 1998).

Using loss on heating method to examine and control the total content of volatile matter in simethicone was specified in the BP (2009): ‘maximum 1.0%, determined on 1.00 g by heating in an oven at 150°C for 2 h, carry out the test using a dish of 60 mm in diameter and 10 mm deep (BP, 2009). However, the analysis method of volatile matter components and their content in simethicone has not been reported in the literature until

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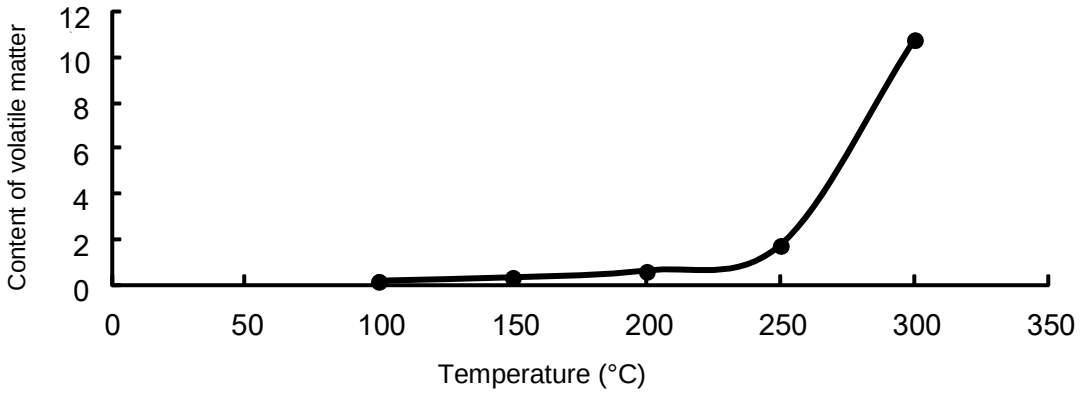

Figure 1. Total count of volatile matter determination result of simethicone sample.

now. Meanwhile, there is few complete mass spectrometry library information available to retrieval. Hence, gas chromatography-mass spectrometry (GC-MS) method (Aghel et al., 2011; Moronkola et al., 2009) was chosen in the present study to analyze the compositions of volatile substances in simethicone crude drug qualitatively and quantitatively. The mass spectrogram and the law of peaks were investigated to show the compositions and contents of each volatile substance. These data provided scientific basis for improving the synthesis process of PDMS, the quality control of simethicone and monitoring the clinical side effects of simethicone.

MATERIALS AND METHODS

Apparatus

QP2010/PLUS GC-MS (equipped with NIST 2.0 mass spectrogram library, Shimadzu International Trading Co., Kyoto, Japan); Mettler Toledo Classic Balance Line AB-S (Mettler Toledo instruments Co. LTD, Switzerland); XCT-1 high-temperature blast oven (Shanghai Yangguang Experimental Instruments Co. LTD, Shanghai, China); AS10200A ultrasonic cleaner (Tianjin automatic science instrument Co. LTD, Tianjin, China).

Reagents

Simethicone reference standard (The content of silicon is 5.1%, 50g, CAT.NO. 1612652, MD LOT JOH301) was purchased from TianJin YiFang S&T Co. Ltd. (ROCKVILLE, USA); simethicone crude drug (Lot 090901) was obtained from Shanxi Xinbaoyuan Pharmaceutical Co. Ltd.; HPLC-grade N-hexane was purchased from Kelong Chemical Reagent Company (Chengdu, China).

GC-MS conditions

The test solution was analyzed by GC-MS. The GC-MS system was operated in the electron ionization (EI) mode at 70 eV, equipped with a DB-5 capillary silica column (30 m × 0.25 mm × 0.25 µm). The temperature program was initiated at 50°C for 2 min, increasing at a rate of 10°C min^{-1} to 300°C, and then the temperature was held for 10 min. Helium was used as the carrier gas and the split ratio was 1: 30. The flow rate was 1.0 ml/min and the injection volume was 1 µl. The vaporization chamber temperature was 300°C, and the ion source temperature was 250°C. The mass scan range was 40 to 600 amu.

Preparation of test solution

Simethicone reference standards and the sample were weighed accurately for defined amount, and dissolved in n-hexane, prepared as 20% (w/v) solutions. Then, the two mixtures were homogenized by being sonicated for 15 min at 25°C.

Determination of the content of the total volatile substances in simethicone

Simethicone sample of 1.00 g were weighed to be heated in an oven for 2 h at 100, 150, 200, 250, 300°C, respectively. The total content of volatile substances was quantitatively measured triplicate at each temperature.

RESULTS

The total content of volatile matter

The content of volatile matter in simethicone samples increased gradually with the increase of temperature. The total content of volatile matter was 0.32% at 150°C, which was lower than 1.0%, and conformed to the standard of BPC (BPC2009). The total content of volatile matter in simethicone samples was 10.78% at 300°C (Figure 1).

The total ion chromatogram of simethicone reference standards and samples

The volatile substances in both simethicone reference standards and samples with the viscosity of 500 centistokes (cs) were analyzed by GC-MS (Figures 2 and

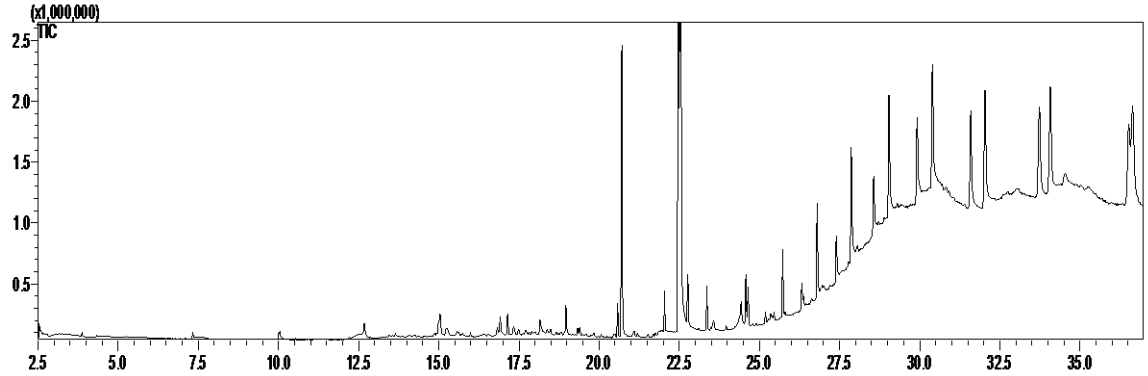

Figure 2. GC-MS total ion chromatogram of volatility components of simethicone reference substance. (x: Retention Time/min; y: Relative Intensity).

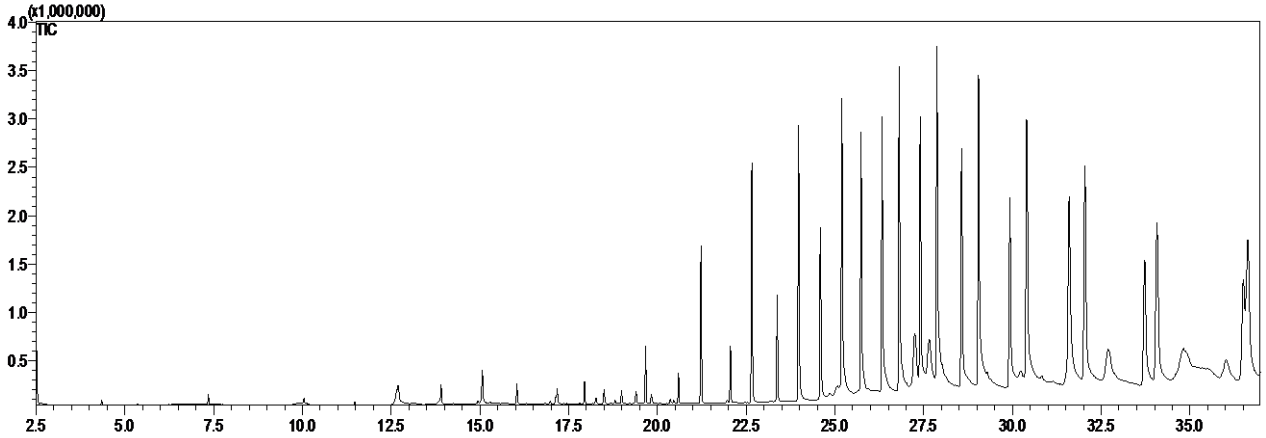

Figure 3. GC-MS total ion chromatogram of volatility components of simethicone sample. (x: Retention Time/min；y: Relative Intensity).

3). The results showed that each volatile matter in simethicone was separated clearly, which provided a premise for the following qualitative and quantitative analysis.

Mass spectrum of the volatile matter in simethicone

The molecular weight of the lower molecular weight volatile components was in the mass scan range (M < 600 doc.). Therefore, they were available through the mass spectra library retrieval. The volatile matter in simethicone samples included two sets of homologous compounds: liner methylpolysiloxane (MD_mM) and cyclic methylpolysiloxane (D_n). The molecular weight of MD_mM series components were: 162, --, --, 384, 458, 532, ...n (MD_1M and MD_2M were not detected) successively (Figure 4A and B); and the molecular weight of D_n series components were: 222, 296, 370, 444, 518, 592, ...n (Figure 4C and D).

The relation between the retention time of lower molecular weight components and the number of structural units

Components whose molecular weights beyond the mass scan range were difficult to acquire qualitative analysis, due to their mass spectrograms not giving clear information. Through the retrieval of mass spectrum library and the resolution of mass spectrum, the two series of homologues of lower molecular weight volatile substances (MD_mM and D_n) in simethicone appeared alternately followed by the retention time found in the present study. Meanwhile, the retention time interval of the two adjacent components in the same series was close. The present result showed that the retention time interval of the two components containing same structural

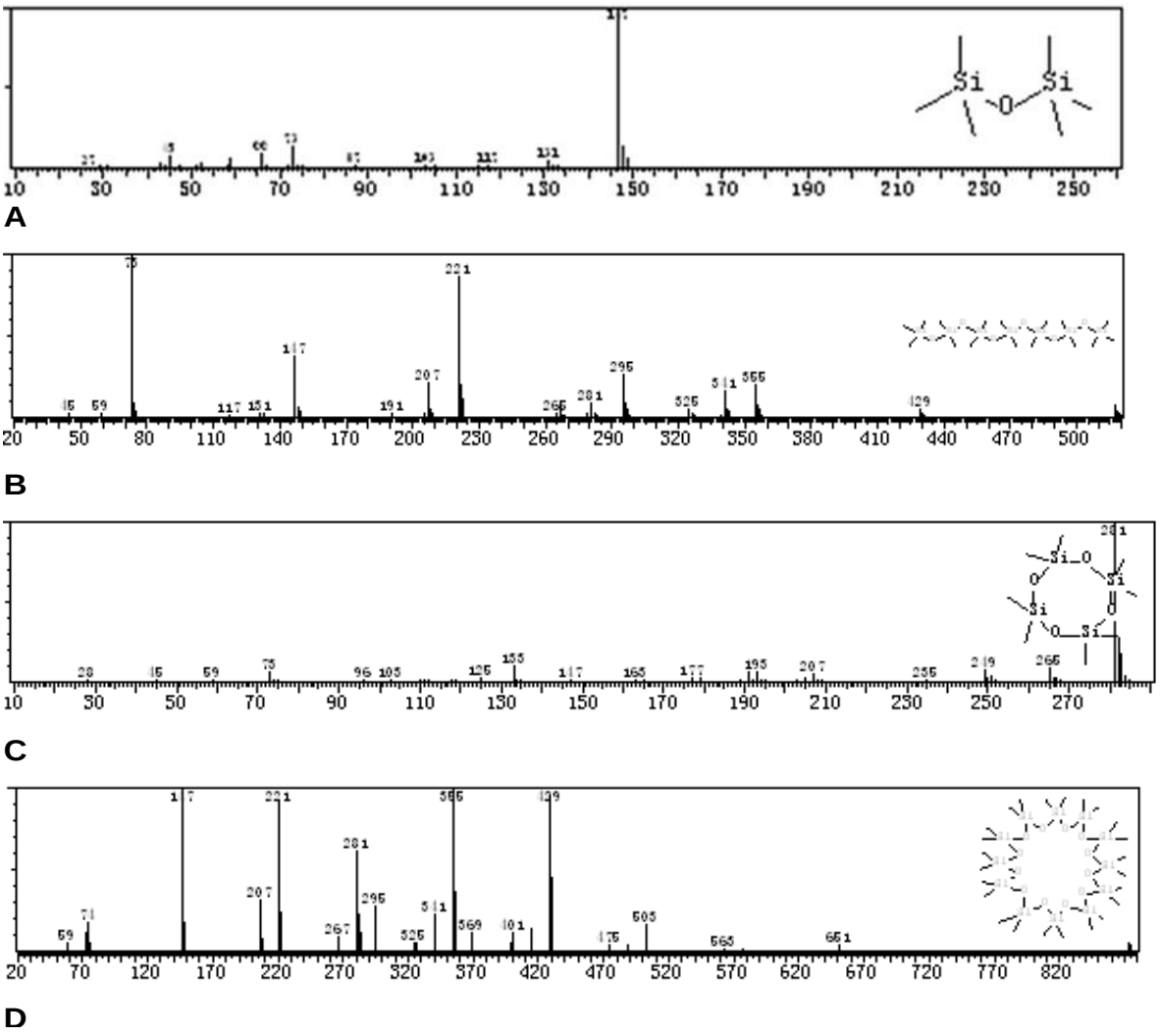

Figure 4. Portion mass spectrograms of MDmM and Dn components (A, MM; B, MD5M; C, D4 and D, D12). (x: m/z; y: Relative Abundance).

units in different series was basically consistent. A diagram is plotted by using the number of structural against the retention time of each component in the two homologues (Figure 5).

Qualitative and quantitative analysis results of GC-MS

The total ion chromatograms of volatile components of simethicone reference standards and samples were searched in the mass spectrum library. The analysis result showed that 42 components were identified, combined with the artificial interpretation of the mass spectrogram and the investigation of the regularity of the peaks, which accounted for 99.21% of the total volatile matter. The components include two sets of homologous compounds: 20 species of linear methylpolysiloxane (MD_mM, MM to $MD_{21}M$, MD_1M and MD_2M were not detected) and 22 species of cyclic methylpolysiloxane (D_n, D_3 to D_{24}) (Table 1).

Each component was quantified preliminary with area normalization method according to the GC spectrogram of simethicone samples (Figure 2). The relative content of each volatile component in simethicone samples were gotten. Linear MD_mM accounted for 46.12% of the total content of volatile matter, and cyclic D_n accounted for 53.09% (Table 1).

DISCUSSION

Mass spectrum characteristics of each volatile matter component

The liner MD_mM and the cyclic D_n, the two sets of

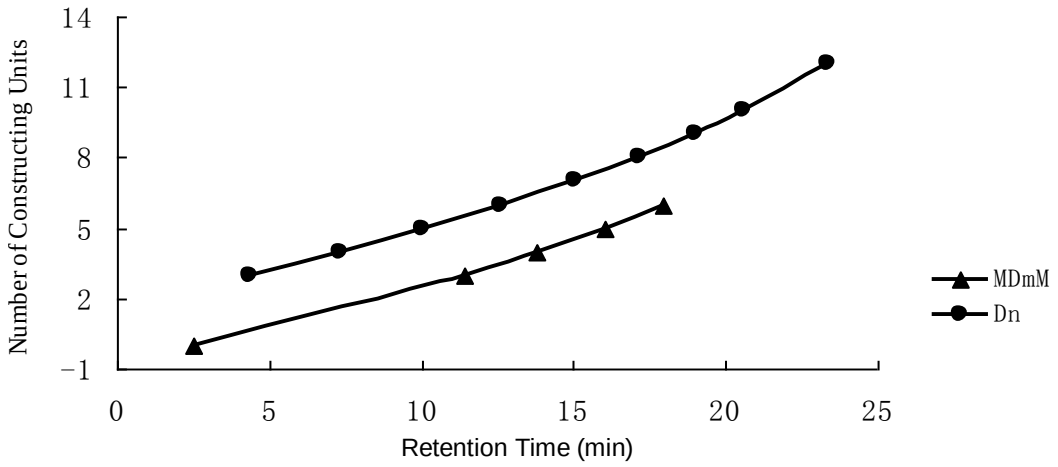

Figure 5. Relation between rentention time and amount of construction units of LMW constituents.

Table 1. GC-MS analytic result of components of volatile matter of simethicone*.

S/N	RT (min)	Structural formula*	MW	Rel. Conc. (%)	S/N	RT (min)	Structural formula*	MW	Rel. Conc. (%)
1	2.538	MM	162	0.02	22	25.732	D_{14}	1036	3.7
2	4.367	D_3	222	0.04	23	26.326	$MD_{12}M$	1050	4.16
3	7.317	D_4	296	0.08	24	26.808	D_{15}	1110	7
4	10.008	D_5	370	0.05	25	27.401	$MD_{13}M$	1124	5.63
5	11.442	MD_3M	384	0.03	26	27.872	D_{16}	1184	5.86
6	12.575	D_6	444	0.49	27	28.566	$MD_{14}M$	1198	3.8
7	13.8	MD_4M	458	0.17	28	29.045	D_{17}	1258	6.14
8	15.008	D_7	518	0.45	29	29.923	$MD_{15}M$	1272	3.95
9	16.041	MD_5M	532	0.2	30	30.232	D_{18}	1332	0.66
10	17.174	D_8	592	0.16	31	30.403	$MD_{16}M$	1346	0.17
11	17.945	MD_6M	606	0.24	32	30.825	D_{19}	1406	6.27
12	18.985	D_9	666	0.16	33	31.593	$MD_{17}M$	1420	5.73
13	19.664	MD_7M	680	0.6	34	32.038	D_{20}	1480	4.95
14	20.592	D_{10}	740	0.31	35	33.723	$MD_{18}M$	1494	5.22
15	21.226	MD_8M	754	1.68	36	34.07	D_{21}	1554	4.68
16	22.055	D_{11}	814	0.63	37	34.592	$MD_{19}M$	1568	0.09
17	22.656	MD9M	828	2.79	38	34.821	D_{22}	1628	1.07
18	23.372	D_{12}	888	1.3	39	34.925	$MD_{20}M$	1642	0.61
19	23.973	$MD_{10}M$	902	3.55	40	36.023	D_{23}	1702	0.99
20	24.587	D_{13}	962	2.61	41	36.499	$MD_{21}M$	1716	2.96
21	25.192	$MD_{11}M$	976	4.52	42	36.628	D_{24}	1776	5.49

*Simple structural formulas were accorded to Wang (2008), MD_mM represented m structural units of D end to end to be a chain structure, M was the terminal group in both sides; D_n represented n structural units of D end to end to be a cyclic structure. M was the terminal group and D was the constitutional unit (Figure 6).

homologous compounds in simethicone, contained the same structural unit of D (Figure 6). The molecular weight difference between the two adjacent components in each series was 74, which was the molecular weight of the structural unit of D [-Si $(CH_3)_2O$-)]. Lots of same fragment peaks were found in their mass spectrum, because they were homologues to each other. The fracture mode of each molecule was similar. Series of fragment ions were in mass spectrometry, such as 44 (Si-O), 59 (O-Si-O), 73 (Si-Me_3 or O-Si-Me_2), 87 (O-Si-Me_3), 103 [O -Si (Me_2)-O], etc., which were characteristic mass spectrum fragment ions of PDMS. The mass spectrum molecular ion peaks

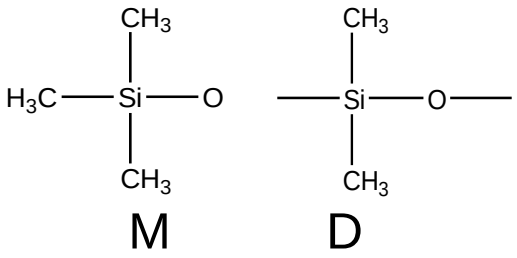

Figure 6. Terminal group M and structural unit D.

of PDMS were very unstable in the EI mode, which were easy to lose a methyl radical to form characteristic fragment ion peaks of $[M-15]^+$ (Jiang et al., 2008; Fu and Wang, 1995).

Qualitative analysis of the volatile substances with higher molecular weight

The components whose molecular weights were beyond the mass scan range were difficult to analyze quantitatively due to the fact that clear information was not given in the mass spectrum. It was evident from Figure 5 that the variation tendency of the retention time in the two sets of homologous was similar. The retention time intervals of the adjacent two components in the same series were close; and the retention time intervals of the two components which contained the same structural units in different series were basically consistent. Therefore, the structures of the volatile substances with higher molecular weight can be inferred from the similarity of the mass spectrums and the regularity of the retention time, and they could be analyzed quantitatively. By analogy, the composition of PDMS can be gotten by combine with the analysis of thermal cracking GC-MS and the study of molecular weight distribution by gel permeation chromatography (GPC).

The content of D_4 and MM

D_4 and MM are the important starting materials for the synthesis of PDMS. So, it can be concluded that the two raw materials were the main components of volatile substances in simethicone. Adalbert et al. (1999) used D_4 and MM as representative to study the intracorporal chemical stability of ocular simethicone after prolonged clinical use. They used GC and GC-MS to detect siloxane oligomers, but no D_4 and (or) MM was detected, so they deemed that simethicone was stable *in vivo* after prolonged clinical use. But Adalbert et al. (1999) did not consider the sensitivity of mass spectrometry and concentrations of D_4 and MM in the human body. The present study used a higher concentration of simethicone (20%, 1.0 µl) to detect D_4 and MM. The result showed that the content was as low as 10^{-7}g • g^{-1}. An adult takes about 80 mg simethicone emulsion one time in clinic, it is possible that D_4 and MM may not be detected after been dispersed into body owning to the sensitivity of mass spectrometry.

The synthesis of PDMS

The components of volatile matter in simethicone reference standards were consistent with those in the simethicone samples, both of them contained two sets of homologous compounds: liner MD_mM and cyclic D_n. The main difference was the content of these components. The peak intensity of the same component in simethicone reference standards was smaller than that of simethicone samples, with the same injection volume. The result suggested that the content of each volatile component was lower than that of simethicone samples.

In addition, we found that the volatile components in simethicone samples contained some catalysts from the synthesis of PDMS through GC-MS analysis, which were unsaturated fatty acid, unsaturated fatty acid esters, and diethyl phthalate. Different viscosities of PDMS were acquired in the synthesis process by changing the ratio between D_4 and MM. The smaller the MM proportion is the greater the viscosity will be. Consequently, the synthesis technology and purification methods of simethicone samples is able to be improved, such as increasing the temperature and prolonging the time of wiping off the low-boiling-point substances, to reduce the content of volatile substances of simethicone crude drug. These substances with low boiling point can be used as raw material for the synthesis of silicone after fractionation and removal, or producing fumed silica after been transformed into useful single siloxane by pyrolysis (Pu, 2002).

The main findings of this paper are that the components of volatile matter in simethicone crude drug were analyzed qualitatively and quantitatively by GC-MS. In conclusion, 42 components were identified, which accounted for 99.21% of the total volatile matter, including two sets of homologous compounds: 20 species of linear methylpolysiloxane (MD_mM, MM to $MD_{21}M$) and 22 species of cyclic methylpolysiloxane (D_n, D_3 to D_{24}). The results of this research provided a scientific basis for improving the synthesis process of PDMS, quality control of simethicone and clinical monitoring of simethicone's side effects.

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