INTERNATIONAL MEDICAL UNIVERSITY

MALAYSIA

BACHELOR OF PHARMACY

FORMATION OF LIPOGELS FROM LIQUID PARAFFIN AND ALUMINUM STEARATE

TAY YUAN SHEN
BP215
00000019683

ASSOCIATE PROF. KANG YEW BENG

NOVEMBER 2018

Acknowledgements

First and foremost, I would like to thank my supervisor, A/P Kang Yew Beng for the advice and guidance throughout this research. I managed to learn more on research and learn different kind of laboratory skills as well as gaining more knowledge. Furthermore, I, wish to express my gratitude to my parents for financially supporting me throughout my degree and especially during the research. Lastly, I would like to show my appreciation towards my groupmate, Kong Sing Hung for helping me throughout this semester.

Approval Sheet

I, the supervisor to Tay Yuan Shen hereby certify that the dissertation revisions have been made based on the recommendations by the Examiners.

Signature

ASSOCIATE PROF. KANG YEW BENG

(Date) 22/2/19

Declaration

I hereby declare that the dissertation is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at the International Medical University or any other institution.

Signature

TAY YUAN SHEN
00000019683
(DATE) 22/2/19

1.0 Abstract

Lipogels are monophasic lipid-based semisolid used for transdermal drug delivery. Currently, there are not many lipophilic transdermal systems available in the market which is the ideal nature for transdermal drug delivery. Hence, more studies should be done to improve lipogels. Conventional lipogels are using magnesium stearate and liquid paraffin to form where the magnesium stearate is the gelling agent and liquid paraffin is the oil component. Most studies done are targeted on the oil component but in this study, we are targeting the gelling agent and replacing magnesium stearate with aluminum stearate which is also an alkaline metal but having a higher charge in its salt form. The lipogels are formed by heating the mixture of liquid paraffin and 1-10% aluminum stearate in an oil bath at 130^{o}C for 1 hour with constant stirring. Then, the lipogels are characterised by polarised light microscopy, differential scanning calorimetry, Fourier transform infrared spectroscopy and modified Brinell test. From the results obtained, semisolid lipogels can be formed with 2-9% aluminum stearate. When a higher amount of aluminum stearate is used to form the lipogels, the gels formed are harder and starting from 10% aluminum stearate, the gels formed are solid state. The product formed with 1% aluminum stearate has a liquid state.

2.0 Introduction

In recent years, topical drug delivery has become a favourable system for drug delivery and many developments has been carried out to improve the drug delivery and reduce skin irritation (1). Topical drug delivery is a commonly used route of administration for drugs as it provides localised effects and it avoids first-pass metabolism. Besides, topical drug delivery is also a favourable route of administration as it is convenient and affordable (1). Due to the lipophilic nature of the stratum corneum, the best topical drug delivery requires delivery systems of a lipophilic nature (2). One of the lipophilic topical delivery system is the lipogel. Lipogels are a monophasic non-aqueous system which is formed when a stearate-based gelling agent is dispersed in oil which makes it a lipid based system (3). Due to its low content of water, lipogels are non-greasy, self-preserving and has high skin permeability when compared to hydrophilic systems (3). Currently, there are few lipophilic topical delivery systems out in the market. Hence, lipogels which are one of the lipophilic topical delivery systems should be further studied. The few advantages of using lipogels is that it can increase the drug loading, provide sustained release and help maintain a low pH inside the lipogels which is ideal for drugs (4).

Conventional lipogels uses magnesium stearate as the gelling agent and will be dispersed in liquid paraffin. Magnesium stearate is used as the gelling agent due to their lubricating, separating, water repelling and gelling properties (5). On the other hand, liquid paraffin is used as the oil component as it is easily obtained, safe and cheap (6). In this study, magnesium stearate will be replaced with aluminum stearate as the gelling agent where 1-10% of aluminum stearate will be dispersed in liquid paraffin to form the lipogel. Aluminum is an alkaline metal just like magnesium so, it has similar properties to magnesium which are the lubricating, separating, water repelling and gelling properties but the difference is that the salt of magnesium has a charge of 2^+ whereas the salt of aluminum has a charge of 3^+ (5). Due to

the properties of aluminum stearate, it is used as additives for paints and lubricants (7). Besides, aluminum stearate is also used widely in the cosmetic industry as it has surfactant properties which allows it to stabilise emulsions (8).

This research is based on Khalid Ahmad Sheikh's research where he formed lipogels with liquid paraffin and 12.5% magnesium stearate (3). His methodology used to form lipogels originated from Scric *et al* who prepared the initial stearate-based lipogel and that methodology will be used in this research (9). Fong Chee Weng further studied on Khalid Ahmad Sheikh's research by replacing the oil component of the lipogel which is liquid paraffin with palm olein and palm stearin (10). Hence, most studies so far had targeted the oil component of the lipogels rather than the gelling agent which is the main reason behind this research.

3.0 Materials and Methods

3.1 Methodology

3.1.1 Formation of the Lipogel

First, 1-10% w/w aluminum stearate was placed in a 500mL beaker containing liquid paraffin. The mixture was stirred with an overhead stirrer and was heated in an oil bath until it reaches 130^{o}C. The temperature was maintained at approximately 130^{o}C for 1 hour while being stirred continuously with an overhead stirrer at 200rpm. Then, the mixture was left to cool to room temperature.

3.1.2 Characterisation of the Lipogels

The lipogels was characterised using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and a hardness test and visually characterised by

polarised light microscopy. Polarised light microscopy is used to observe the microstructures of aluminum stearate and lipogels prepared and the magnifications used are x40, x100 and x400. The DSC was used to analyse the thermal characteristics of liquid paraffin, palm olein and the prepared lipogels. The heating cycle of the DSC was set at 25-120^{o}C and at a rate of 8^{o}C/min. The samples were scanned at 32 continuous scans with Happ-Genzel apodisation and resolution at 4cm^{-1} from 4000-600cm^{-1} with the FTIR. The hardness of the lipogels will be tested with a modified Brinell test (3). A ball bearing was dropped from a height of 15cm from the lipogels and the indent on the lipogels were measured.

3.2 Materials

The materials used are aluminum stearate and liquid paraffin. The aluminum stearate is purchased from the company, Honeywell Riedel-de Haen® and the liquid paraffin is purchased from the company, Merck. Both the aluminum stearate and liquid paraffin were manufactured in Germany. The apparatus used are the DSC, FTIR, hot plate, overhead stirrer and the microscope. The DSC used was the DSC 823 Mettler Toledo. The FTIR used was from the company Shimadzu with the model IRAffinity-1S. The microscope used was from Nikon Type 104. The overhead stirrer used was the RW16 basic from the company IKA-Werke. Lastly, the hotplate used was from Daihan Labtech.

4.0 Results

4.1 Visual Appearance

The lipogels were prepared with different concentrations of aluminum stearate and liquid paraffin ranging from 1-10% w/w of aluminum stearate. After heating with constant stirring, the lipogels formed had a different physical state and after cooling the lipogels some changes in the visual appearance could be observed. The physical state of the lipogels after heating and after cooling can be seen in Table 2. After heating, all the lipogels had some flowability but as it cools down, the lipogels harden and loses its flowability. Only the lipogels formed with 1% aluminum stearate had flowability after cooling down. After one week, syneresis could be observed in the lipogels formed with 2%, 3% and 4% aluminum stearate.

Aluminum stearate used (%w/w)	Physical state after heating	Physical state after cooling
1	Liquid	Liquid
2	Liquid	Semisolid
3	Liquid	Semisolid
4	Liquid	Semisolid
5	Semisolid	Semisolid
6	Semisolid	Semisolid
7	Semisolid	Semisolid
8	Semisolid	Semisolid
9	Semisolid	Semisolid
10	Semisolid	Solid

Table 2: Physical state of lipogels with different concentration of aluminum stearate used after heating and after cooling. Liquid state is where the product has good flowability and looks homogenous. Solid state is where the product has no flowability. Semisolid state is where the product has some flowability and has a gel-like appearance.

4.2 Hardness Test

The lipogels were subjected to hardness test 1 hour after cooling. The indent in the lipogels can be seen in Table 2. The lipogels formed with 1% aluminum stearate was not tested as it was a liquid. The lipogels formed with 7-10% aluminum stearate had no changes when tested with the hardness test.

Aluminum stearate used (%w/w)	**Indent of lipogels measured (mm)**
1	-
2	3
3	3
4	2
5	1
6	1
7	0
8	0
9	0
10	0

Table 2: Indent of lipogels after the hardness test

4.3 Fourier Transform Infrared Spectroscopy

The lipogels were subjected to FTIR after one day of formation and after one week of formation. This is to identify if the syneresis observed affect the physical aspects of the lipogels. The graphs obtained from the FTIR can be found in the Appendix A. The lipogels showed the same peaks when tested after one day and after one week. All the lipogels formed showed similar peaks at 2900cm^{-1}, 1585cm^{-1}, 1450cm^{-1}, 1380cm^{-1}, 983$cm^{-1}$and 720cm^{-1} except for the

lipogels formed with 1% aluminum stearate. No peak could be seen with the lipogel formed with 1% aluminum stearate at 1585cm^{-1} and 983cm^{-1}.

4.4 Microscopy

The lipogels were viewed under normal microscopy and polarised light microscopy one day after formation and one week after formation. This is to identify if the syneresis observed affect the physical aspects of the lipogels. When viewed under the microscope, many black dots and needle-like structures can be seen. More of these structures can be observed when a higher concentration of aluminum stearate was used to form the lipogels. Examples of the structures when viewed under normal microscope can be seen in Figure 1 and when viewed under polarized light microscopy can be seen in Figure 2.

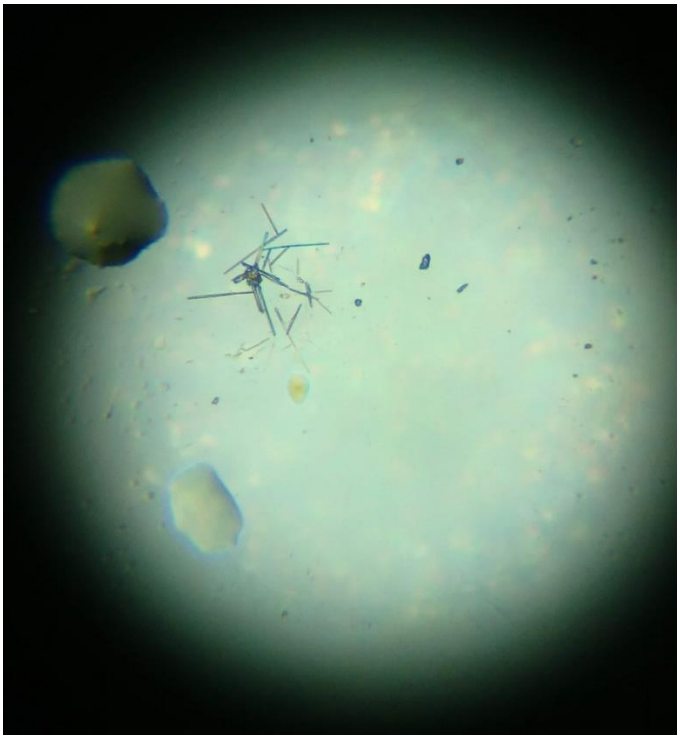

Figure 1: Lipogel formed with 3% aluminum stearate when viewed with normal microscopy at x100 magnification

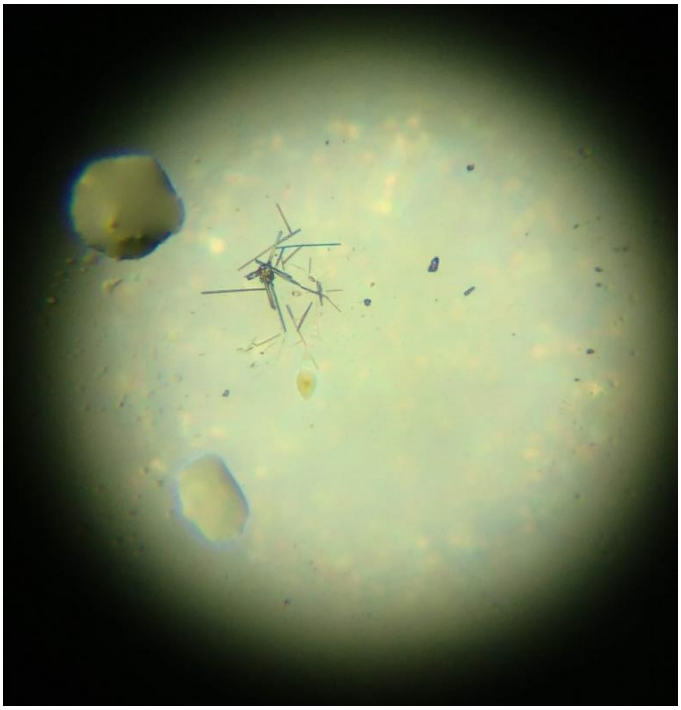

Figure 2: Lipogel formed with 3% aluminum stearate when viewed with polarized light microscopy at x100 magnification

4.5 Differential Scanning Calorimetry

The lipogels formed were subjected to DSC after one week of formation. The graphs obtained from the DSC can be found in Appendix B. The lipogels formed have a similar endotherm at around 108^{o}C when heated and similar exotherm at 72^{o}C when cooled. A sharper and more distinct peak can be observed in lipogels formed with higher percentage of aluminum stearate. However, the DSC graph for the lipogel formed with 10% aluminum stearate is different from the DSC graph of the other lipogels formed. The DSC graph for the lipogel formed with 10% aluminum stearate showed a sloping baseline whereas the other graphs had a flat baseline.

5.0 Discussion

The lipogels were formed with aluminum stearate from 1-10% w/w at 1% intervals. From the results obtained, 1% aluminum stearate is unable to form lipogels. A semisolid lipogel can be formed successfully by using 5-9% aluminum stearate which can be seen in Table 2. Based on the visual appearance and the hardness test of the lipogels formed, a higher percentage of aluminum stearate used will form a harder and more solid lipogel. When using 2-4% aluminum stearate, the lipogels will only be semisolid after cooling down while using 10% aluminum stearate will only form semisolid lipogels at high temperature. Compared to the work done by Khalid *et al*, 12.5% magnesium stearate was needed to form semisolid lipogels (3). Hence, a lower amount of gelling agent is required to form semisolid lipogels by replacing magnesium stearate with aluminum stearate. Besides, a lower amount of gelling agent is needed to form a harder product. This is because aluminum salt has a 3^+ charge while magnesium stearate only has a 2^+ charge. The 3^+ charge allows aluminum salt to form a three-tail bond with stearic acid to form aluminum stearate while the 2^+ charge of magnesium salt only allows it to form a two-tailed bond with stearic acid (11,12). Hence, aluminum forms a stronger and more stable bond with stearic acid which results in better properties (13).

Based on the FTIR results, the lipogels formed with 2-10% showed similar peaks at 2900cm^{-1}, 1585cm^{-1}, 1450cm^{-1}, 1380cm^{-1}, 983cm^{-1} and 720cm^{-1} which reflects the formation of liquid paraffin and aluminum stearate. The FTIR spectrum of aluminum stearate shows peaks at 2900cm^{-1}, 1585cm^{-1}, 1450cm^{-1}, 1380cm^{-1}, 983$cm^{-1}$and 720cm^{-1} whereas liquid paraffin shows peaks at 2900cm^{-1}, 1450cm^{-1}, 1380cm^{-1} and 720cm^{-1} (14,15). The product formed with 1% aluminum stearate did not have a peak at 1585cm^{-1}which is the carboxylate ion (16). This shows that that the carboxylate ion functional group is absent and is broken during the formation of the product. Since the product formed with 1% aluminum stearate has

a liquid state, it can be said that the carboxylate ion functional group might be essential for the formation of a semisolid lipogel.

In the microscopy, many needle-like structures could be observed which may represent the α-crystalline lamellar structures (17). The microscopic results suggest that a higher concentration of aluminum stearate used will produce more lamellar structures which shows a stronger bond and structure. Lamellar structures are also known as lipid bilayers where the polar headgroups are facing the aqueous phase on both sides of the bilayer and the long hydrocarbon chains are opposing each other inside the bilayer (18). Hence, the microscopic results correlate with the hardness test and visual appearance of the lipogels as a harder lipogel is formed with a higher concentration of aluminum stearate.

The DSC results shows that the peaks are more distinct when a higher amount of aluminum stearate is used. This show that the phase change is more obvious when a higher aluminum stearate is used. On the other hand, the lipogel formed with 10% aluminum stearate had a sloping baseline which shows constant enthalpy change throughout the heating and cooling process. This shows that there is a constant phase change in the lipogel. Hence, the results from the DSC also correlate with other tests carried out on the lipogels. The lipogel formed with 10% aluminum stearate has a solid state so the DSC results suggests that the constant phase change observed is the melting and solidification process. The endotherm at around 108^{o}C when heated shows that the melting point for the lipogels is around 108^{o}C and exotherm at 72^{o}C when cooled shows that the solidification point for the lipogels is around 72^{o}C.

The limitations faced in the study is that there is no access to the rheology, x-ray diffraction, texture analyser and hot stage microscopy. The equipment can tell us more important information on the products formed.

6.0 Conclusion

Semisolid lipogels can be formed with aluminum stearate and liquid paraffin where the concentration of aluminum stearate used is 2-9%. Less amount of aluminum stearate is required to form lipogels when compared to magnesium stearate. Besides, the lipogels formed are harder than the conventional lipogels formed with magnesium stearate. Hence, aluminum stearate can be a replacement to magnesium stearate for lipogels. More studies can be carried out on lipogels formed with aluminum stearate to gather more relevant data such as drug incorporation and characterisation of the lipogels with rheology and texture analyser.

References

1. Singh Malik D, Mital N, Kaur G. Topical drug delivery systems: a patent review. Expert Opin Ther Pat [Internet]. 2016;26(2):213–28. Available from: http://www.tandfonline.com/doi/full/10.1517/13543776.2016.1131267

2. Chang R-K, Raw A, Lionberger R, Yu L. Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products. AAPS J [Internet]. 2013;15(1):41–52. Available from: http://www.springerlink.com/index/10.1208/s12248-012-9411-0

3. Sheikh KA. Formulation and characterisation of the lipogels of magnesium stearate and liquid paraffin. Strathclyde Institute of Pharmacy and Biomedical Science; 2010.

4. Xiong M, Tu S, Wang Y. Lipogel for Drug Delivery. Wisconsin Alumni Research Foundation; 2014.

5. Baerlocher. Baerlocher addictives: metallic stearates [pamphlet]. Unterschleissheim. 2005;

6. Ho KM. Proper Choice of Base of Topical Medicaments. 2006;11(5).

7. US EPA O. Chemical Data Reporting under the Toxic Substances Control Act. [cited 2018 Oct 18]; Available from: https://www.epa.gov/chemical-data-reporting

8. Bergfeld WF, Donald V, Hill RA, Klaassen CD, Liebler DC, Marks JG, et al. Safety Assessment of Amino Acid Alkyl Amides as Used in Cosmetics Status : Scientific Literature Review for Public Comment Release Date : Panel Meeting Date : 2013;

9. Srčič S, Korbar-šmid J, Bukovec P, Jezernik K. The structure investigation of magnesium soap - hydrocarbon system. Drug Dev Ind Pharm. 1985;11(2–3):281–98.

10. Fong CW. Formation and characterisation of stearate-based lipogels. International Medical University; 2014.

11. Aluminum stearate | C54H105AlO6 - PubChem [Internet]. [cited 2018 Oct 18]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Aluminum_stearate#section=Top

12. Magnesium stearate | C36H70MgO4 - PubChem [Internet]. [cited 2018 Oct 18]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/11177#section=Chemical-and-Physical-Properties

13. Kekul FA, Friedrich UG, Union I, Chemistry A. Review of Basic Organic Chemistry. Fire Debris Anal chap 3. 2007;49–83.

14. Stearic acid, aluminum salt. [cited 2018 Oct 18]; Available from: https://webbook.nist.gov/cgi/cbook.cgi?ID=C637127&Mask=80#IR-Spec

15. Sadeghazad A, Ghaemi N. Microbial prevention of wax precipitation in crude oil by biodegradation mechanism. Soc Pet Eng [Internet]. 2003;(SPE 80529):1–4. Available from: http://www.onepetro.org/doi/10.2118/80529-MS

16. Silverstein M.Robert, Webster X. Francis KJD. Spectrometric Identification of Organic Compounds, 7th Edition. Spectrometric Identification of Organic Compounds, 7th Edition. 2005.

17. Murdan S, Gregoriadis G, Florence AT. Novel sorbitan monostearate organogels. J Pharm Sci. 1999;

18. Yeagle PL. Structures of Lipid Assemblies. In: The Membranes of Cells. 2016.

Appendix A: FTIR of Prepared Lipogels

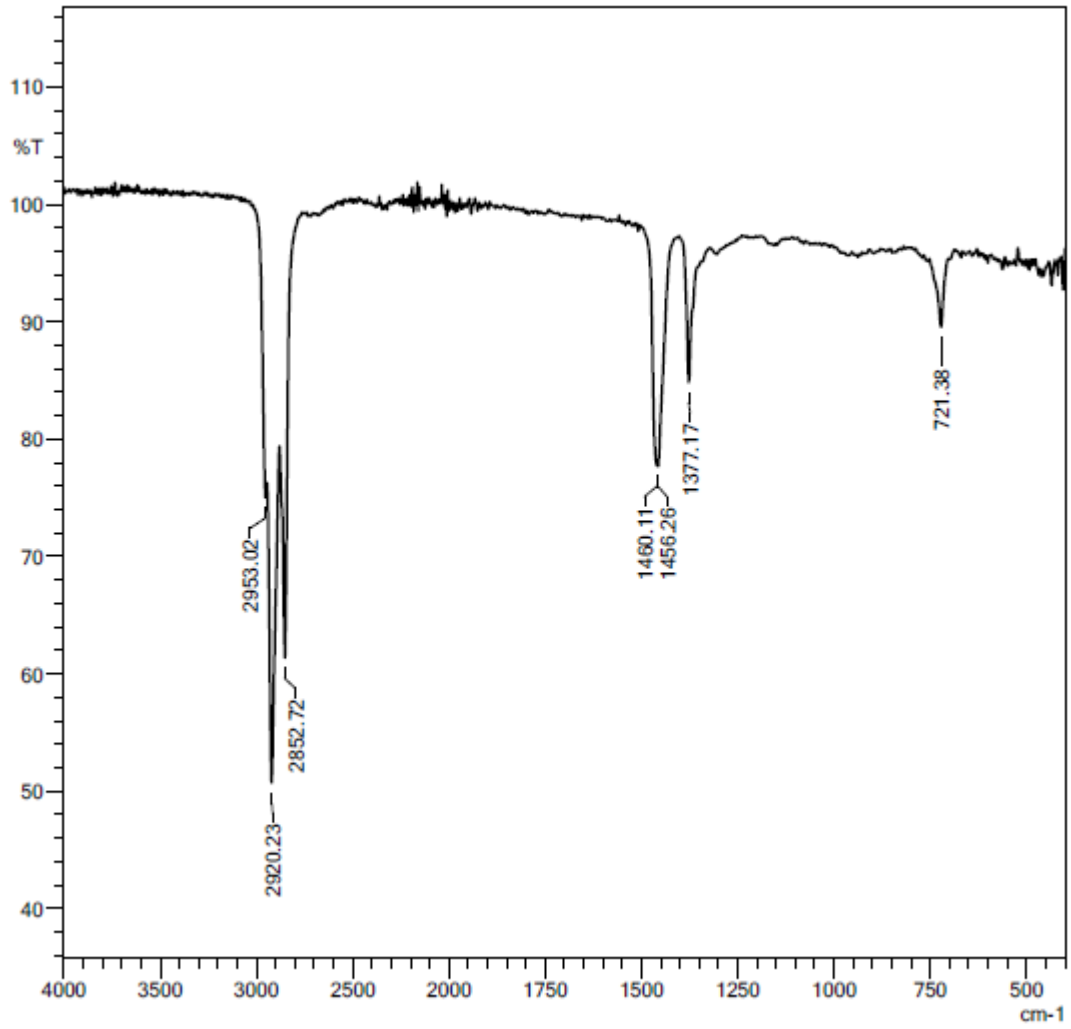

Figure 3: FTIR graph for lipogels formed with 1% aluminum stearate when analyzed after one day

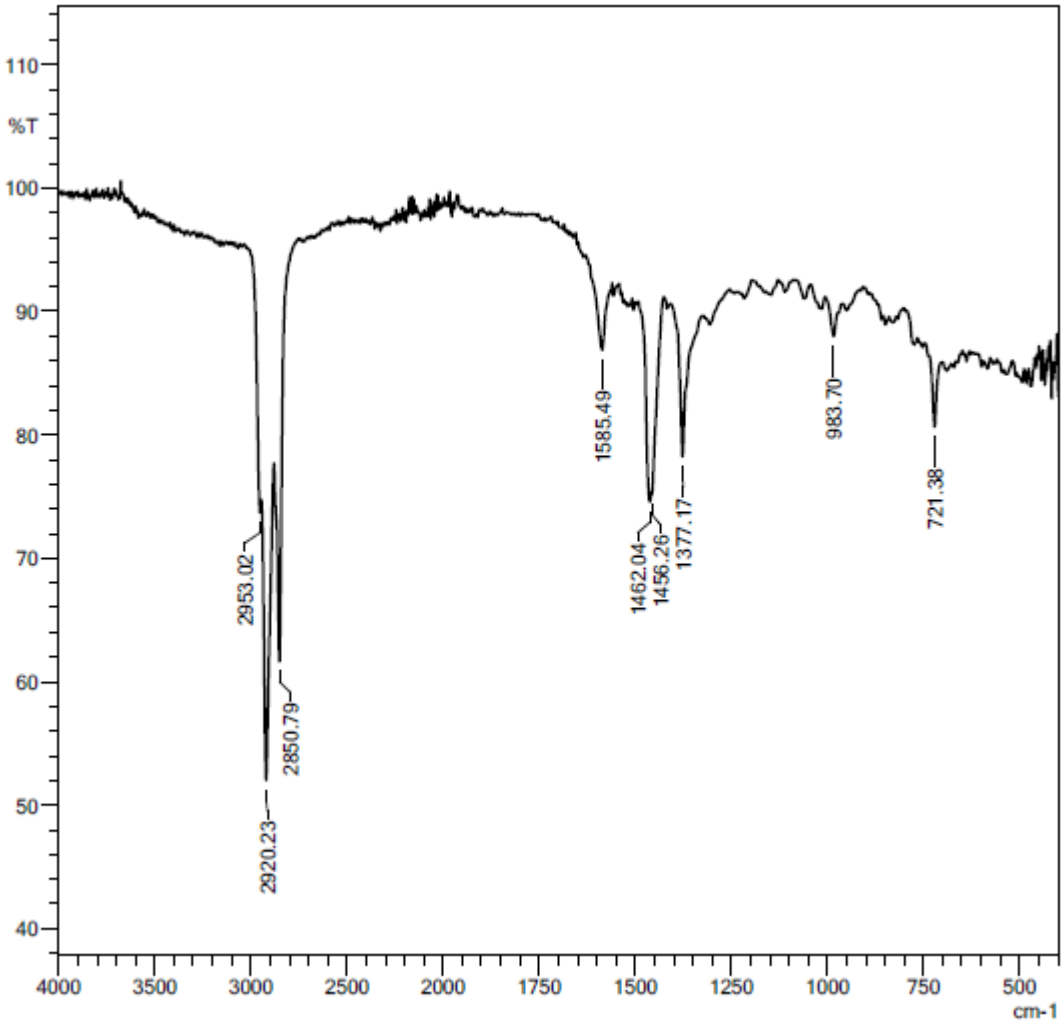

Figure 4: FTIR graph for lipogels formed with 2% aluminum stearate when analyzed after one day

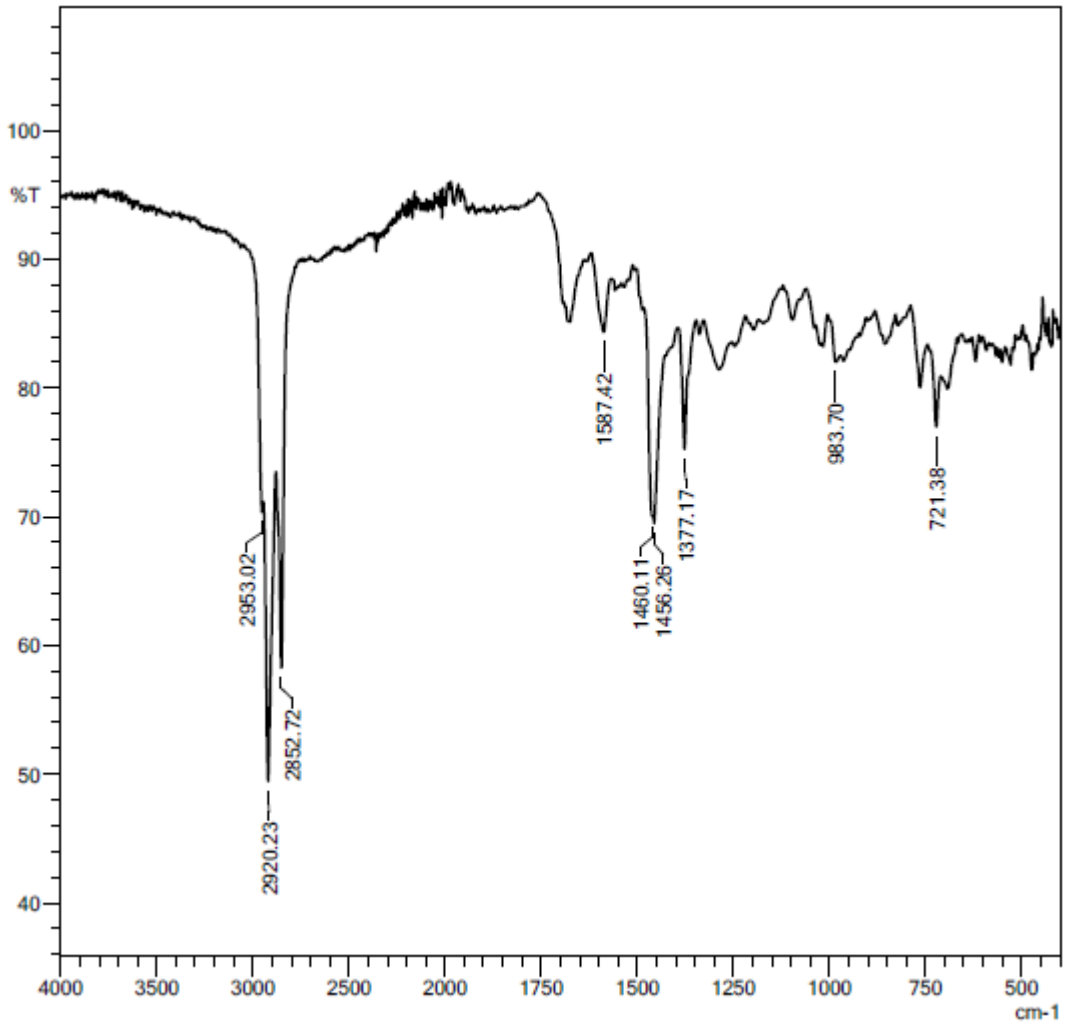

Figure 5: FTIR graph for lipogels formed with 3% aluminum stearate when analyzed after one day

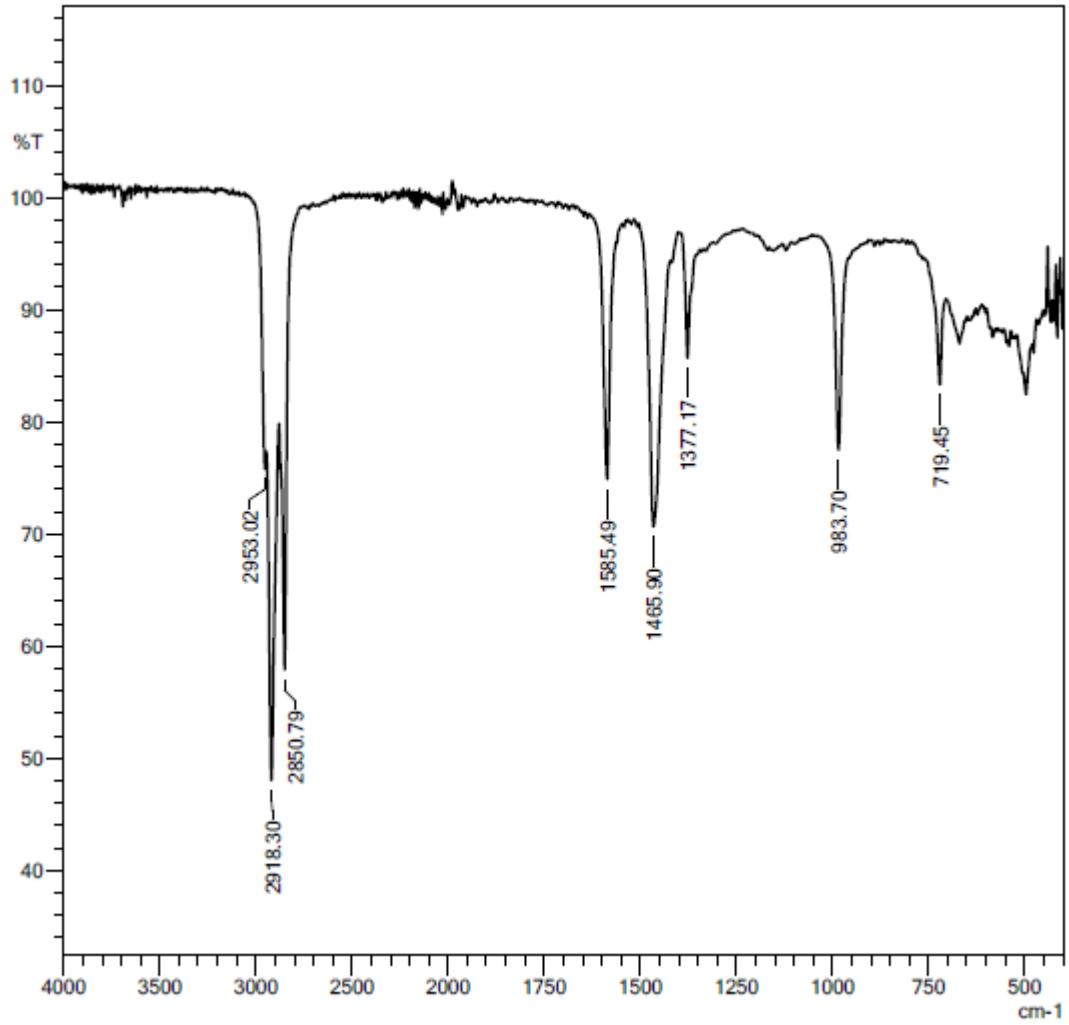

Figure 6: FTIR graph for lipogels formed with 4% aluminum stearate when analyzed after one day

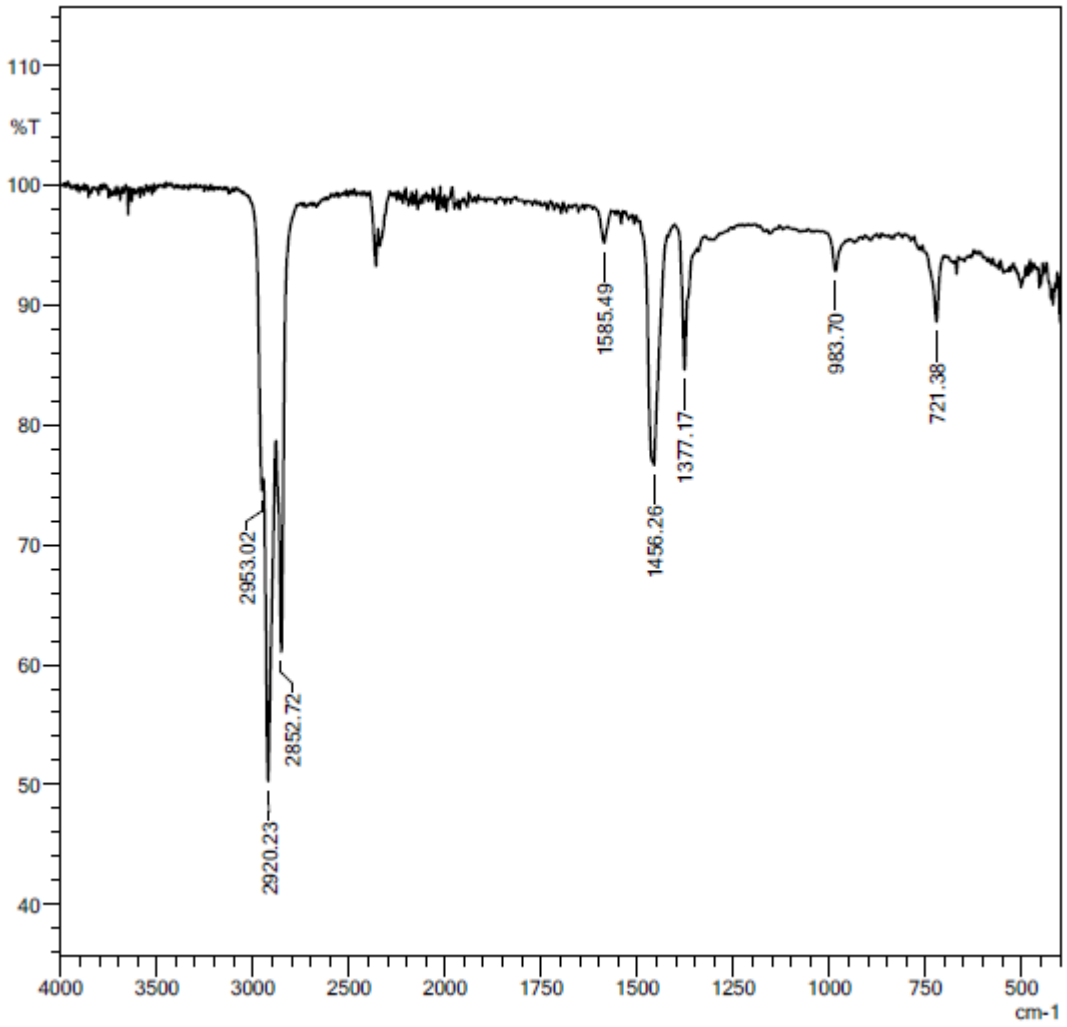

Figure 7: FTIR graph for lipogels formed with 5% aluminum stearate when analyzed after one day

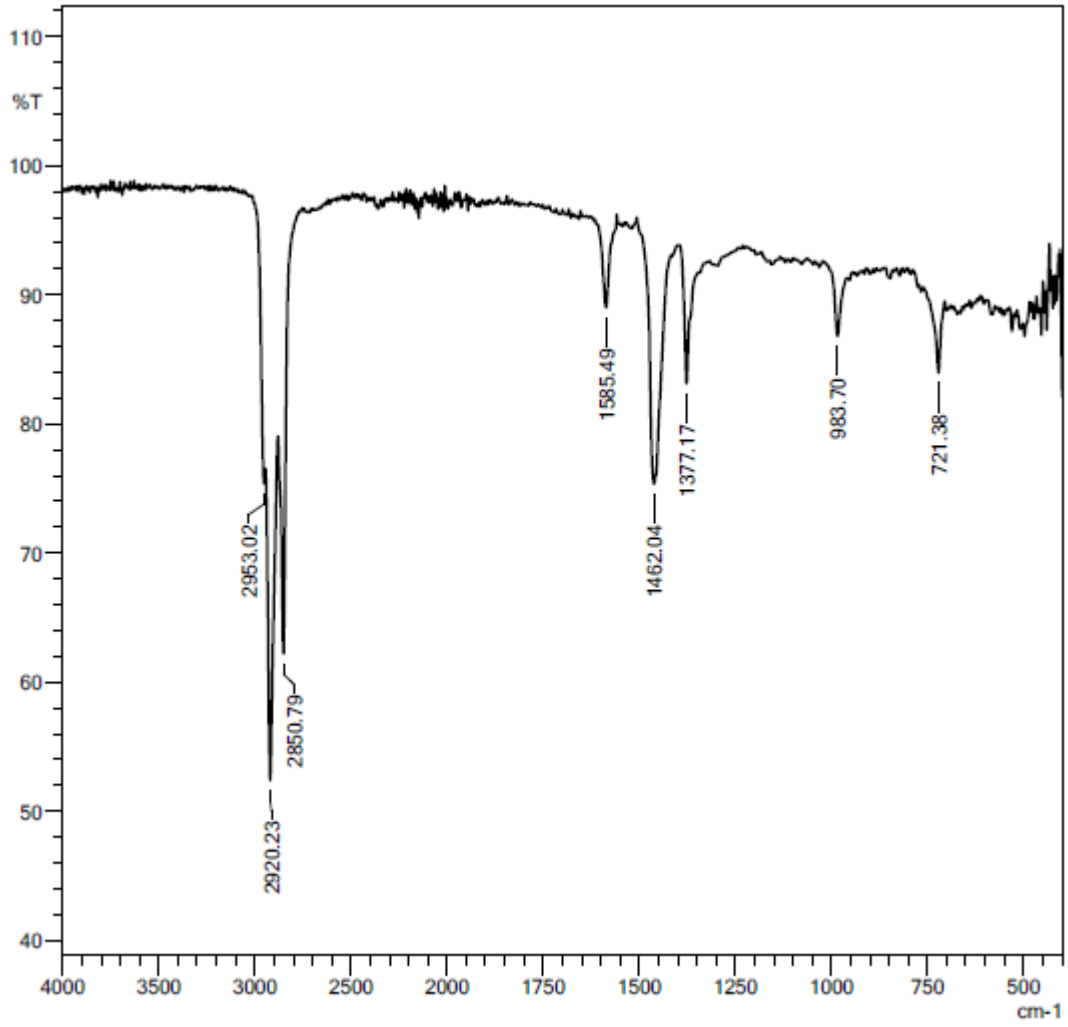

Figure 8: FTIR graph for lipogels formed with 6% aluminum stearate when analyzed after one day

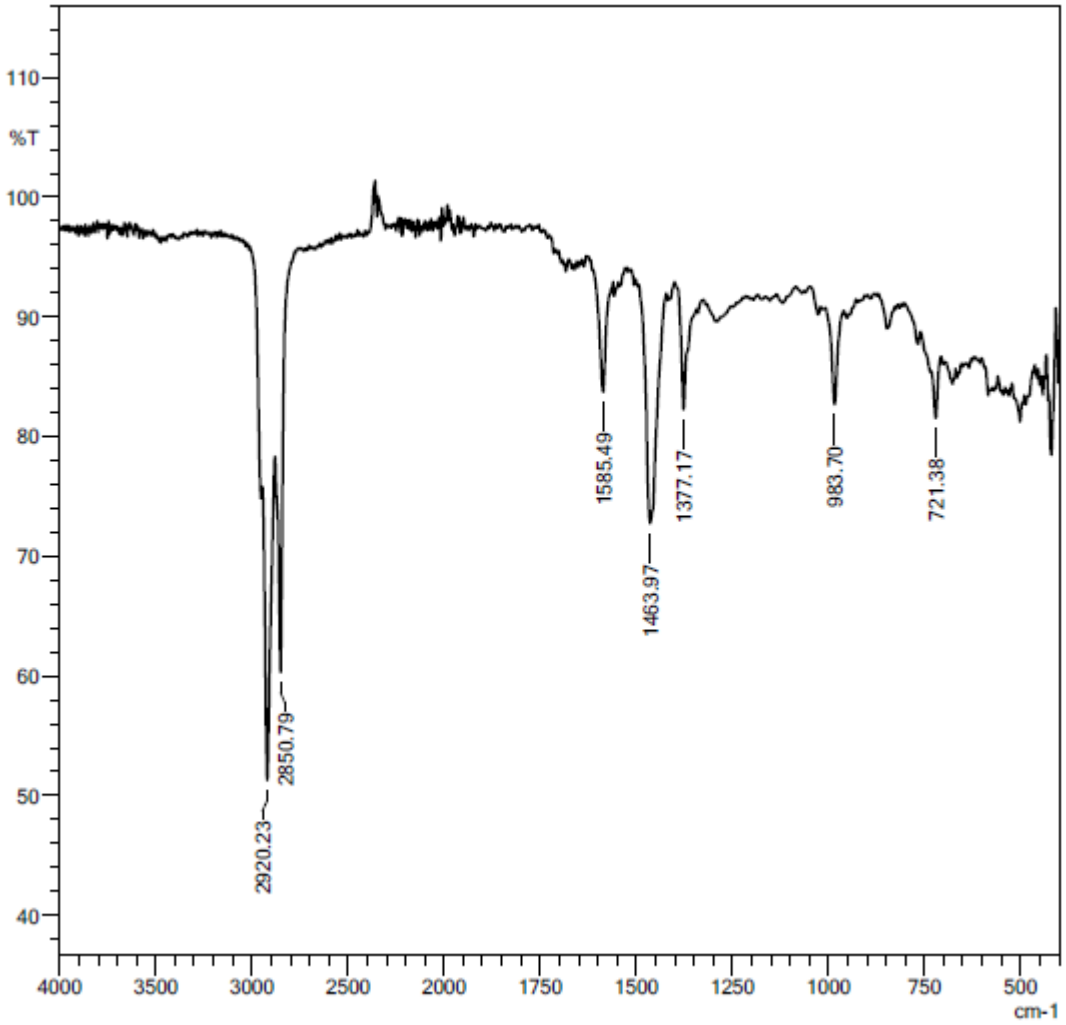

Figure 9: FTIR graph for lipogels formed with 7% aluminum stearate when analyzed after one day

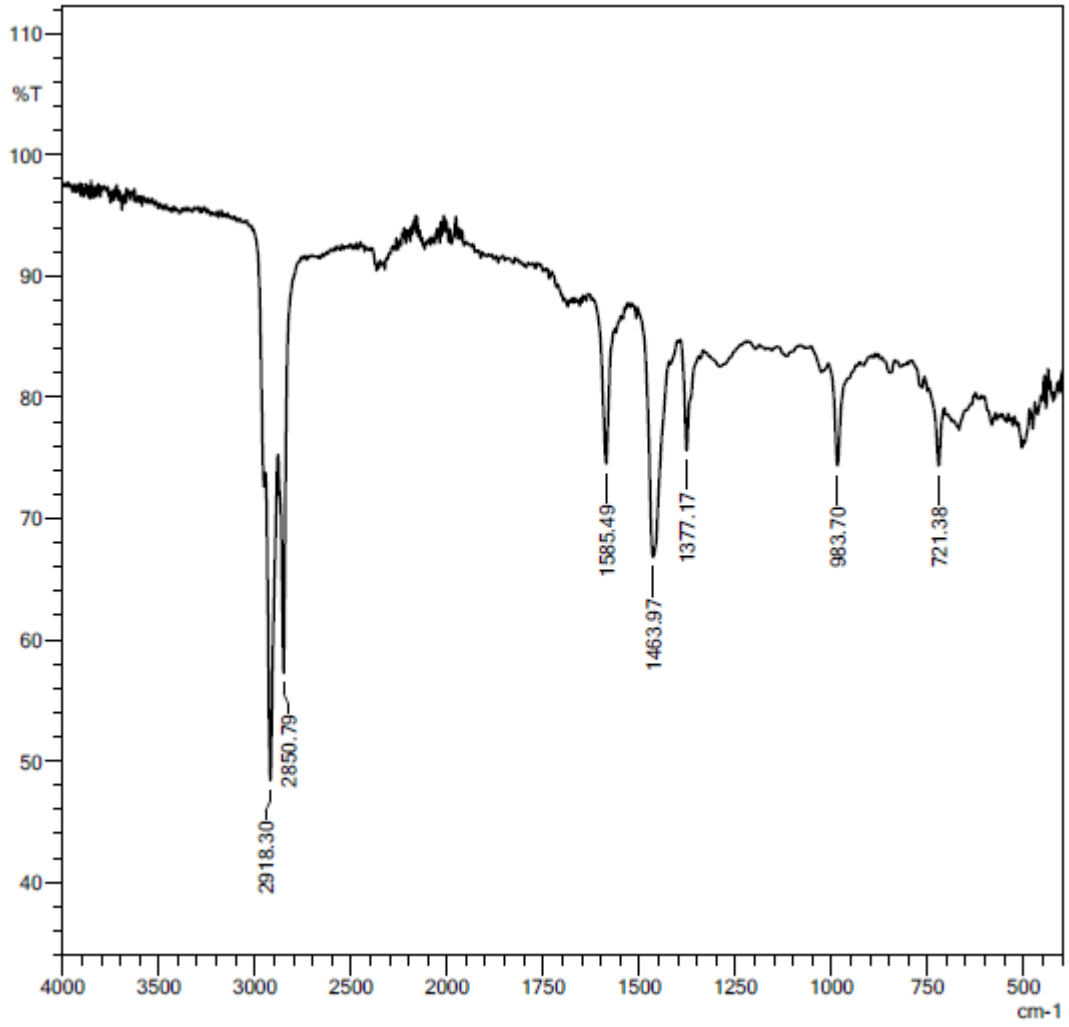

Figure 10: FTIR graph for lipogels formed with 8% aluminum stearate when analyzed after one day

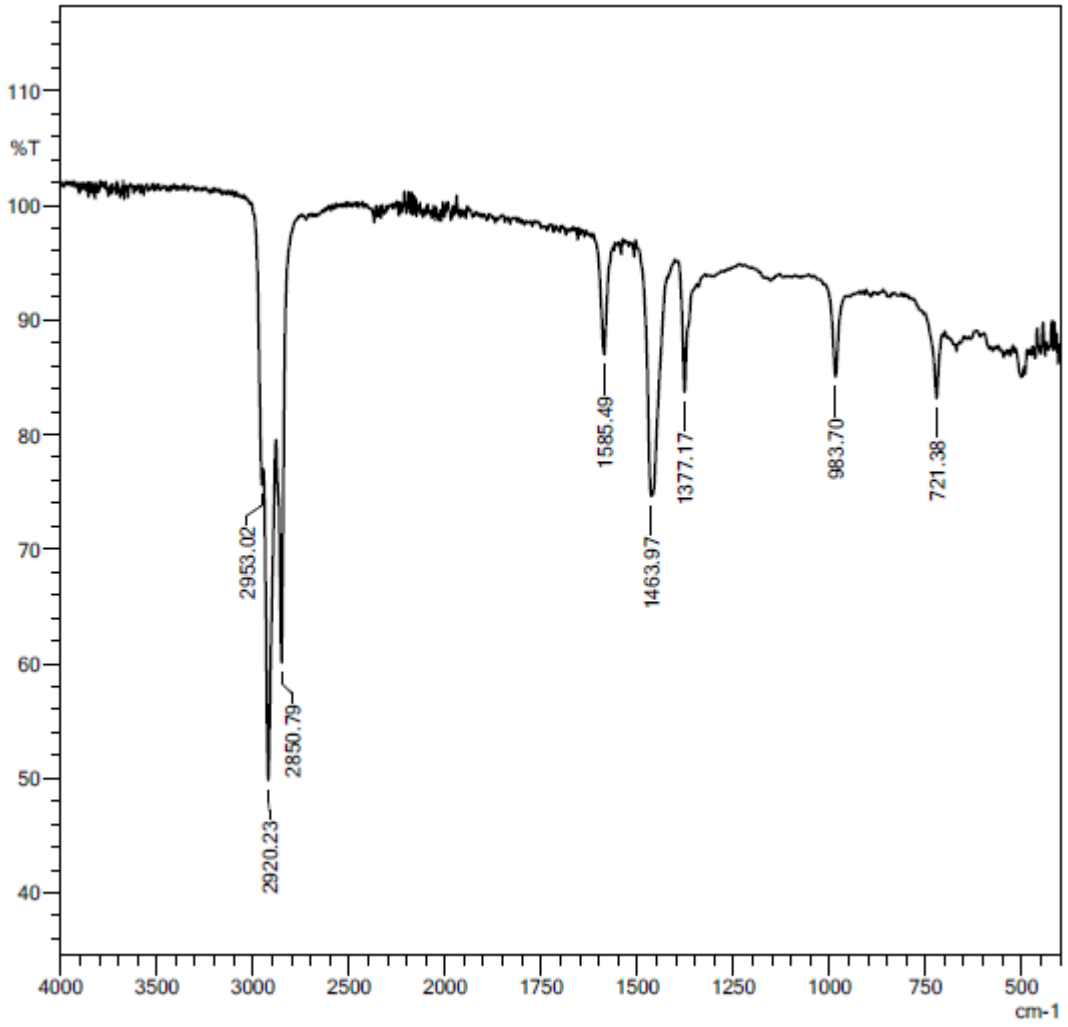

Figure 11: FTIR graph for lipogels formed with 9% aluminum stearate when analyzed after one day

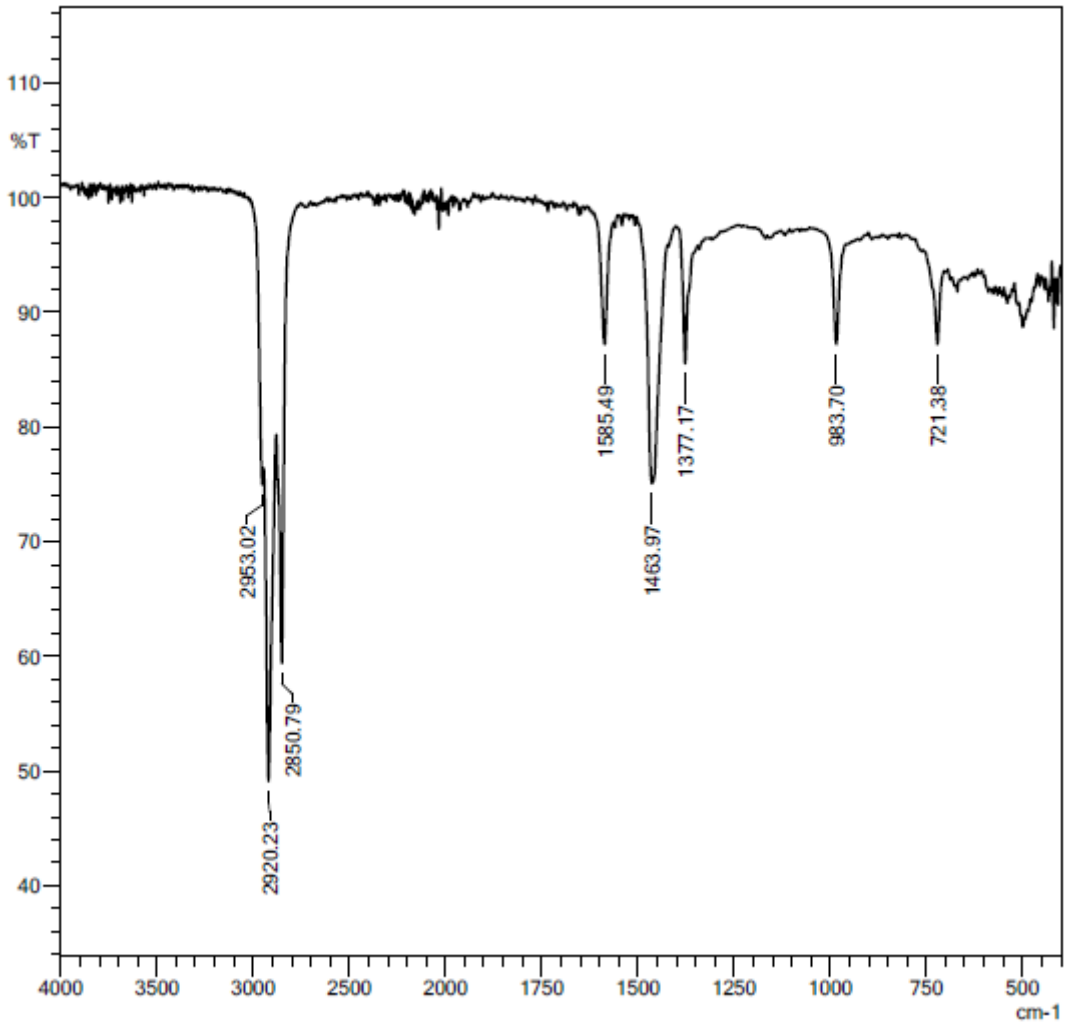

Figure 12: FTIR graph for lipogels formed with 10% aluminum stearate when analyzed after one day

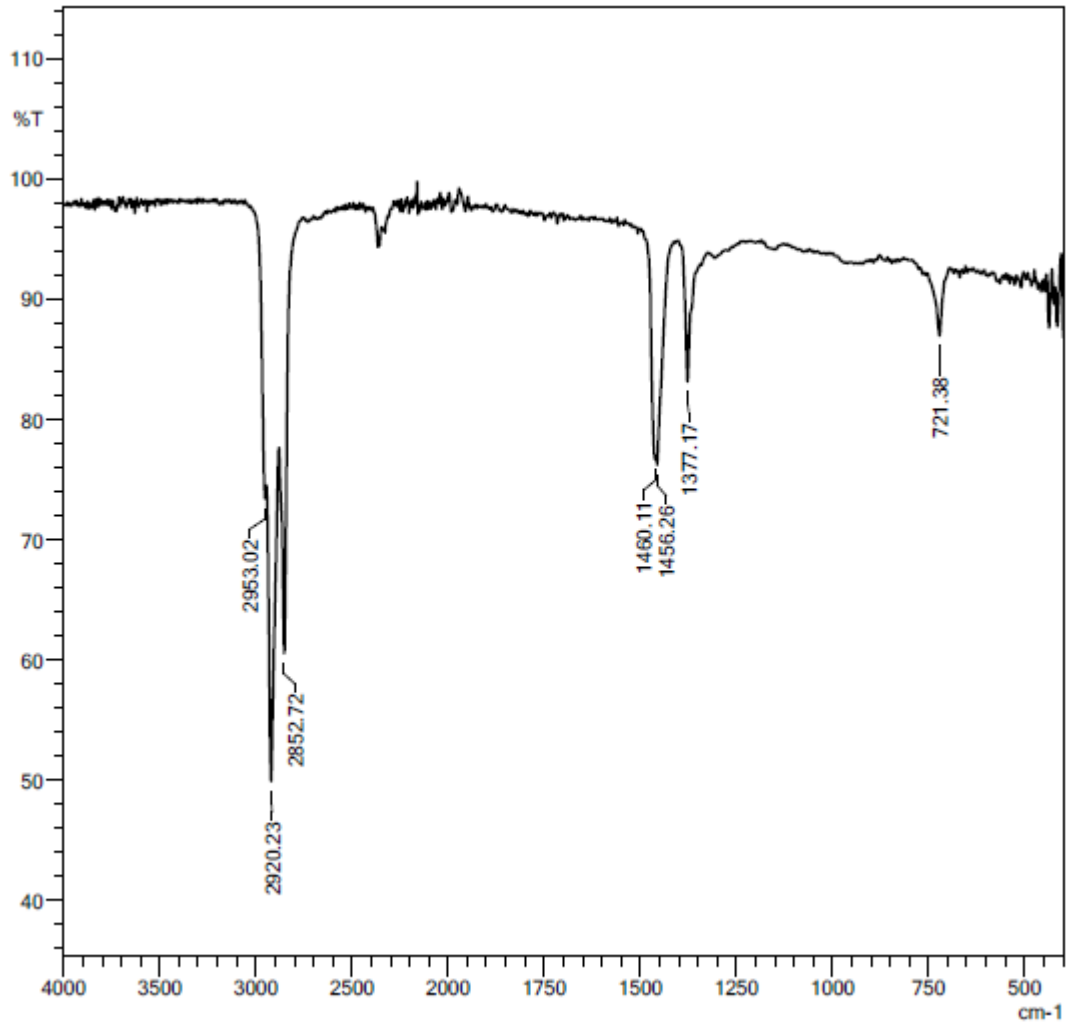

Figure 13: FTIR graph for lipogels formed with 1% aluminum stearate when analyzed after one week

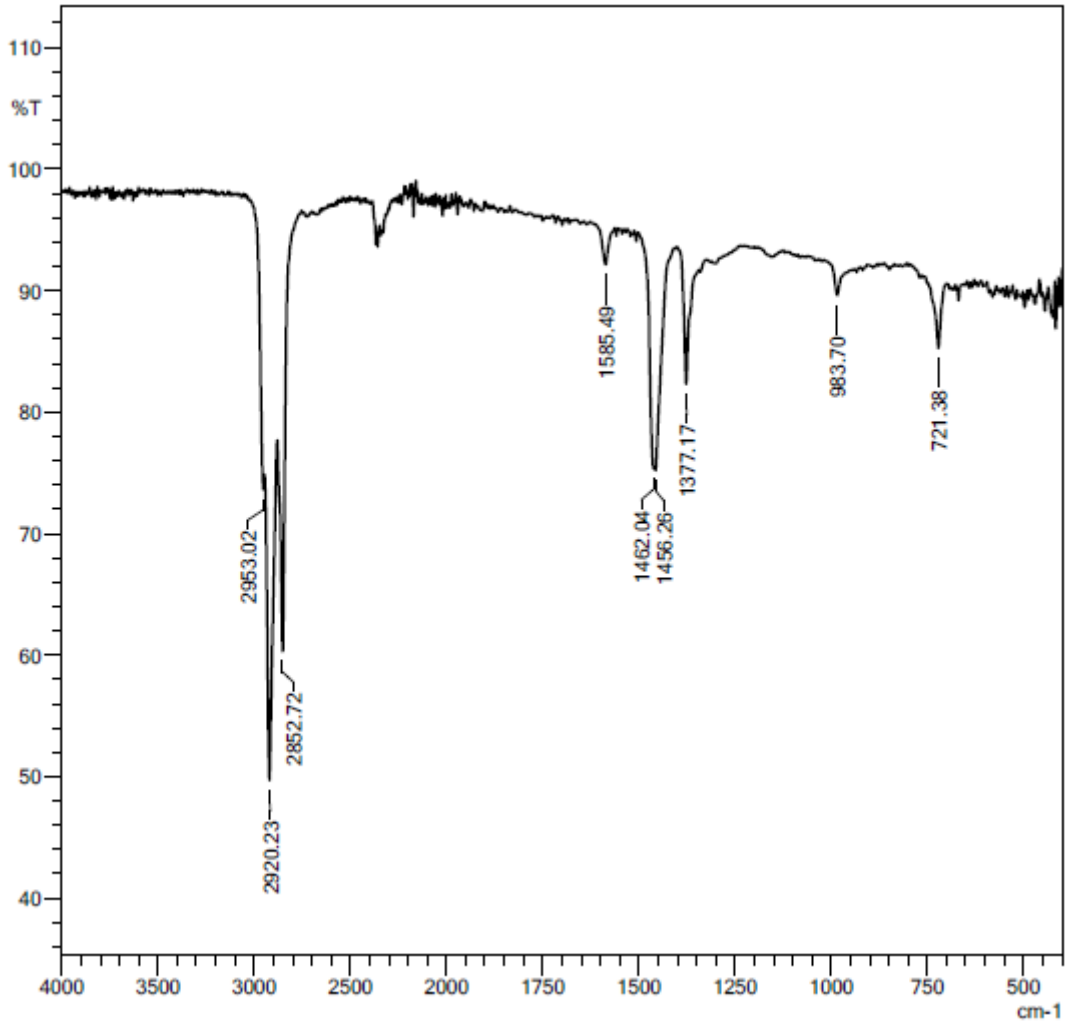

Figure 14: FTIR graph for lipogels formed with 2% aluminum stearate when analyzed after one week

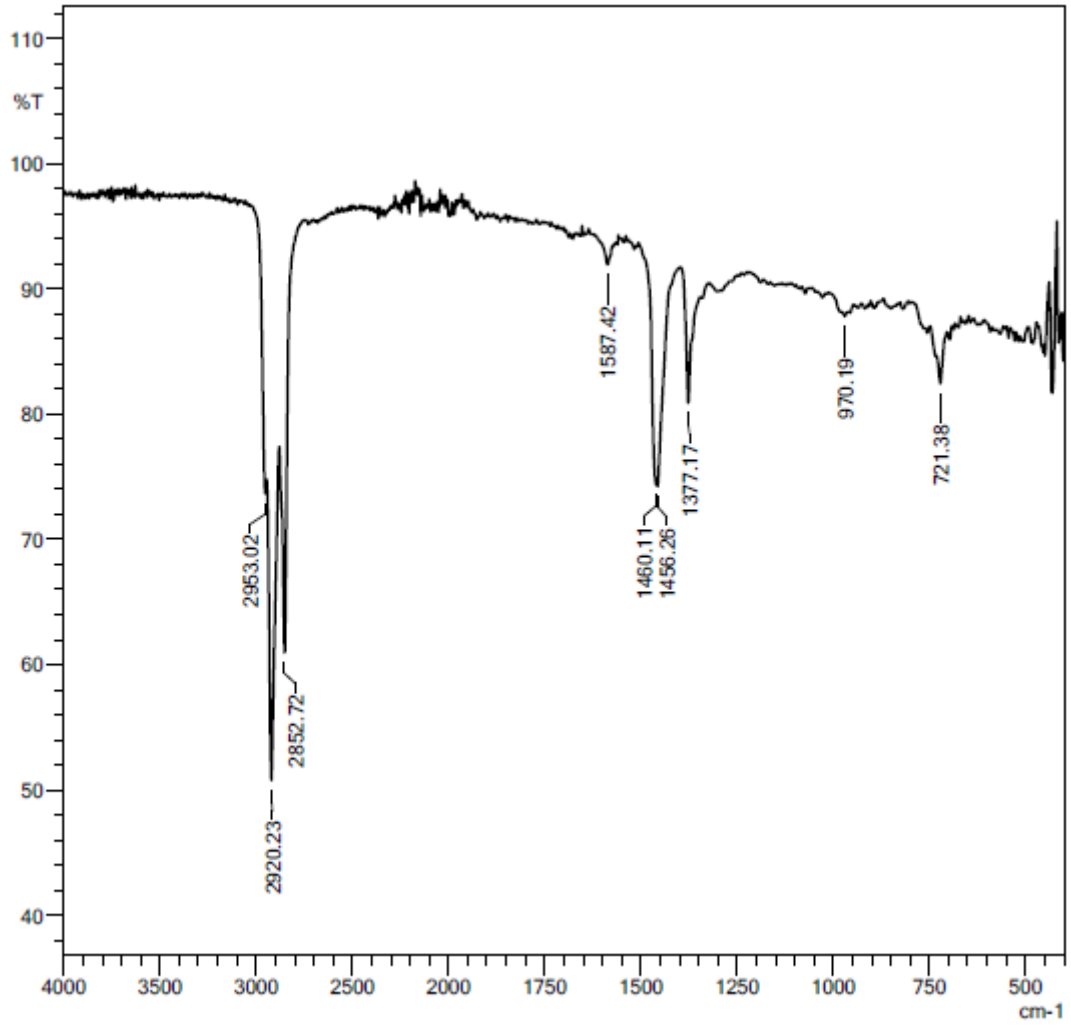

Figure 15: FTIR graph for lipogels formed with 3% aluminum stearate when analyzed after one week

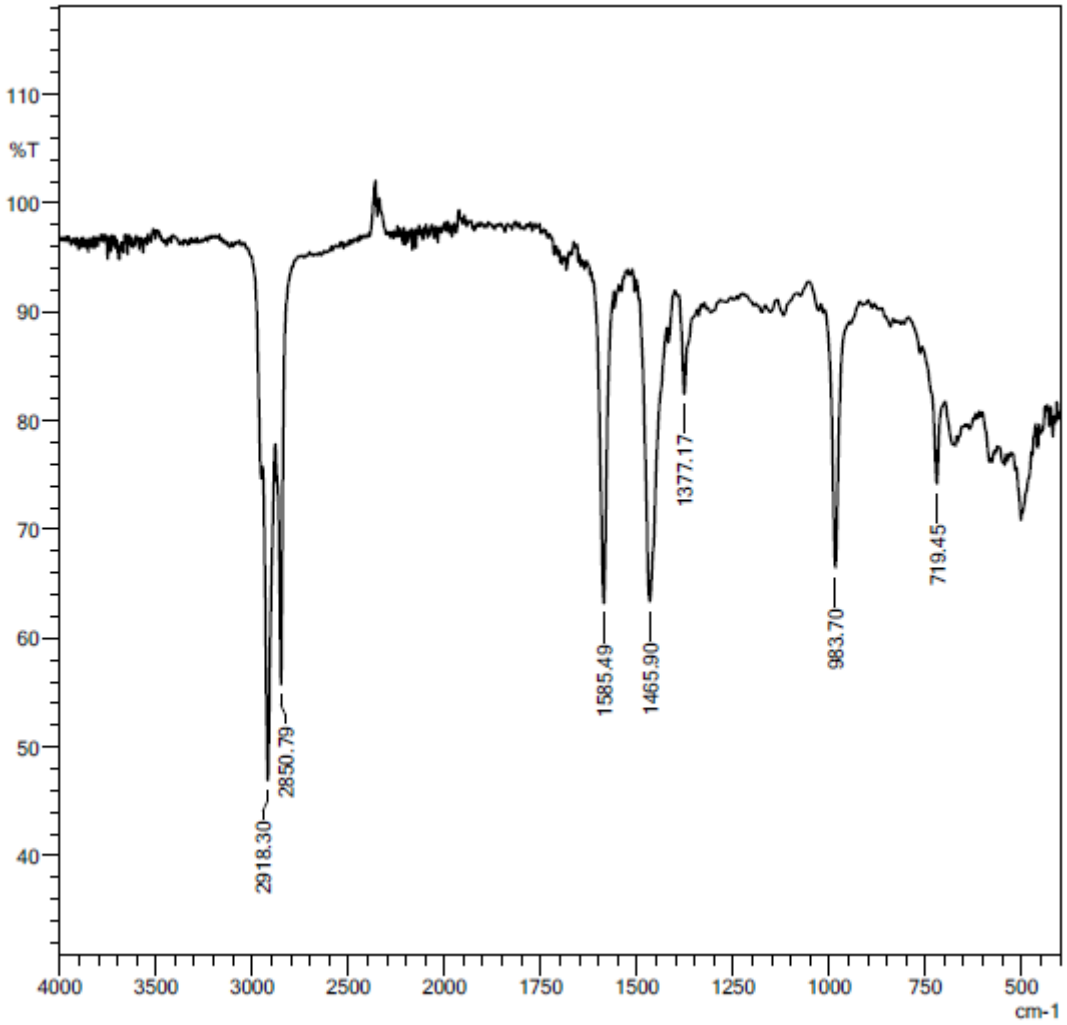

Figure 16: FTIR graph for lipogels formed with 4% aluminum stearate when analyzed after one week

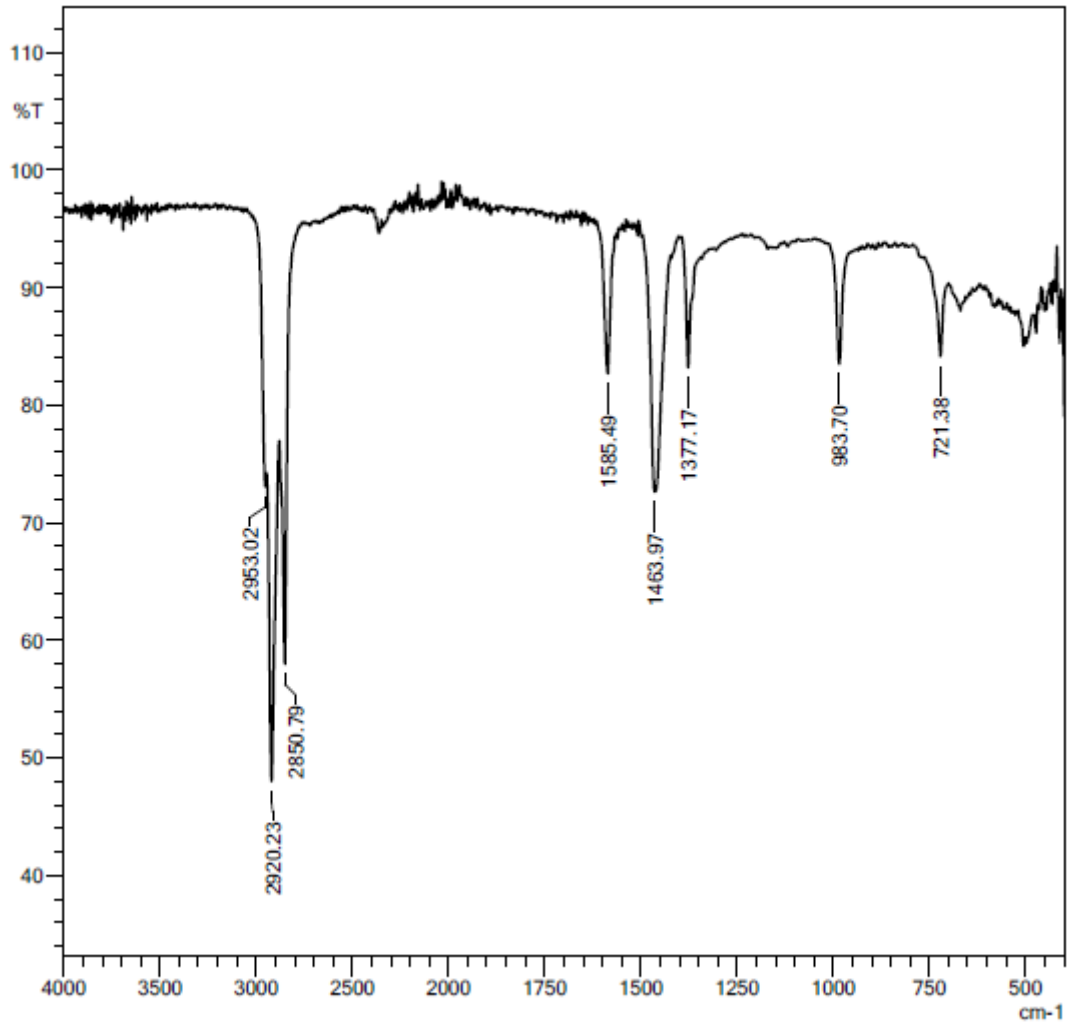

Figure 17: FTIR graph for lipogels formed with 5% aluminum stearate when analyzed after one week

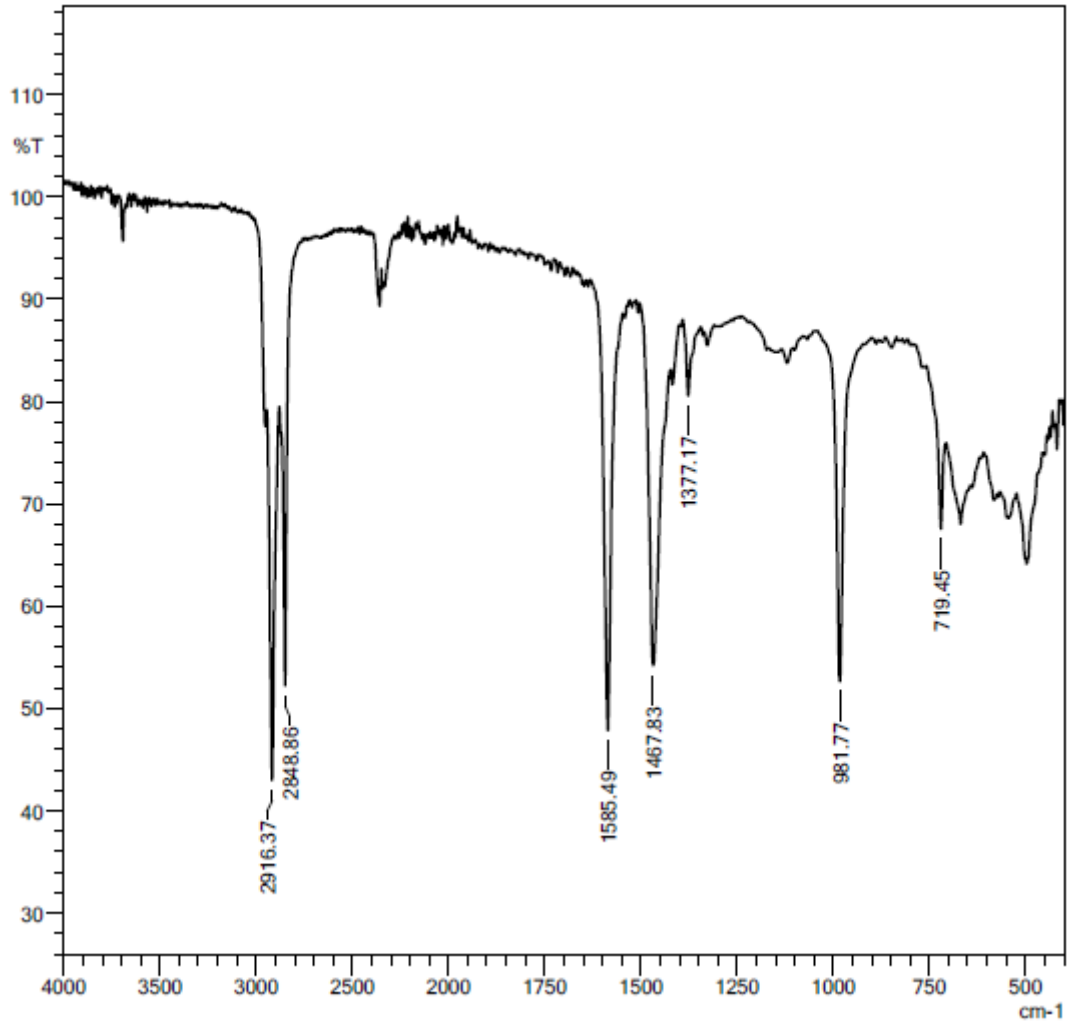

Figure 18: FTIR graph for lipogels formed with 6% aluminum stearate when analyzed after one week

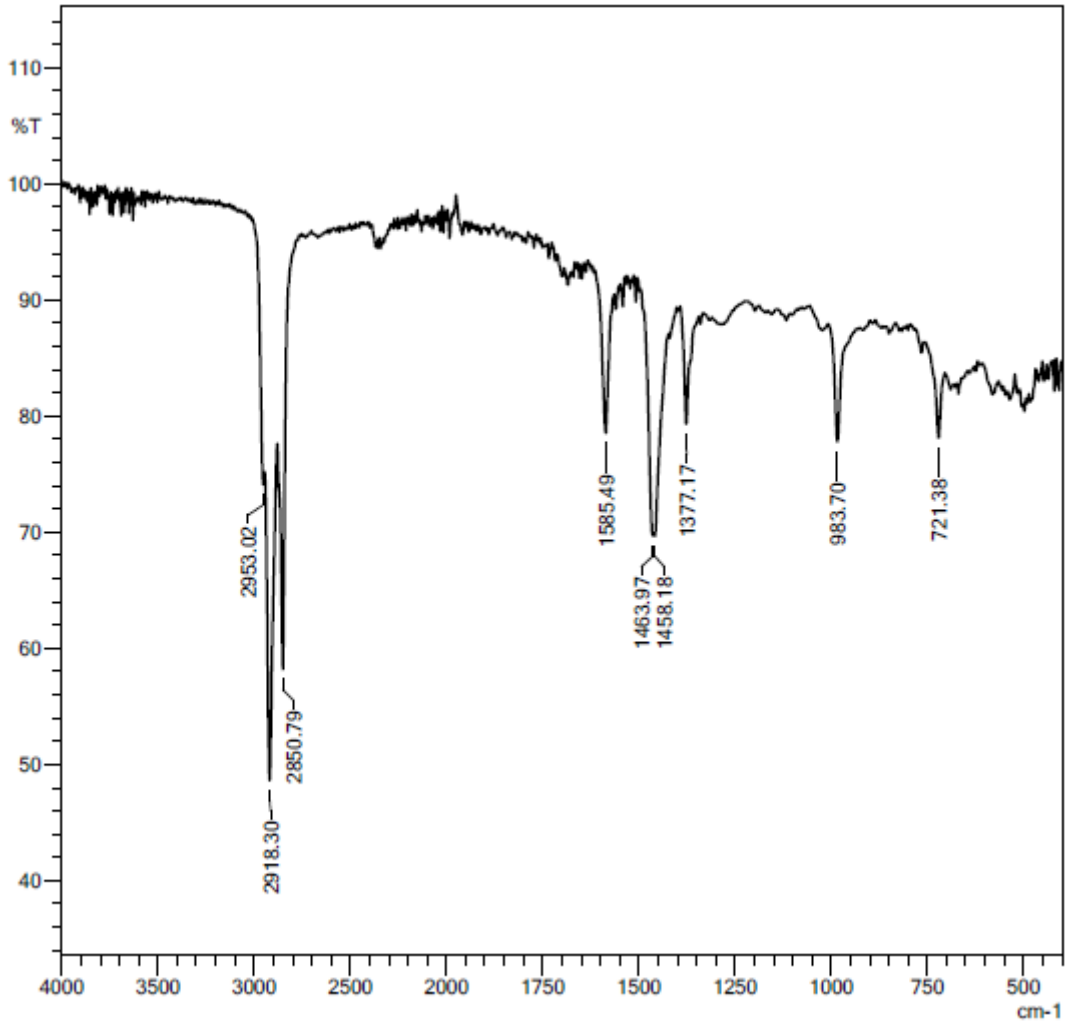

Figure 19: FTIR graph for lipogels formed with 7% aluminum stearate when analyzed after one week

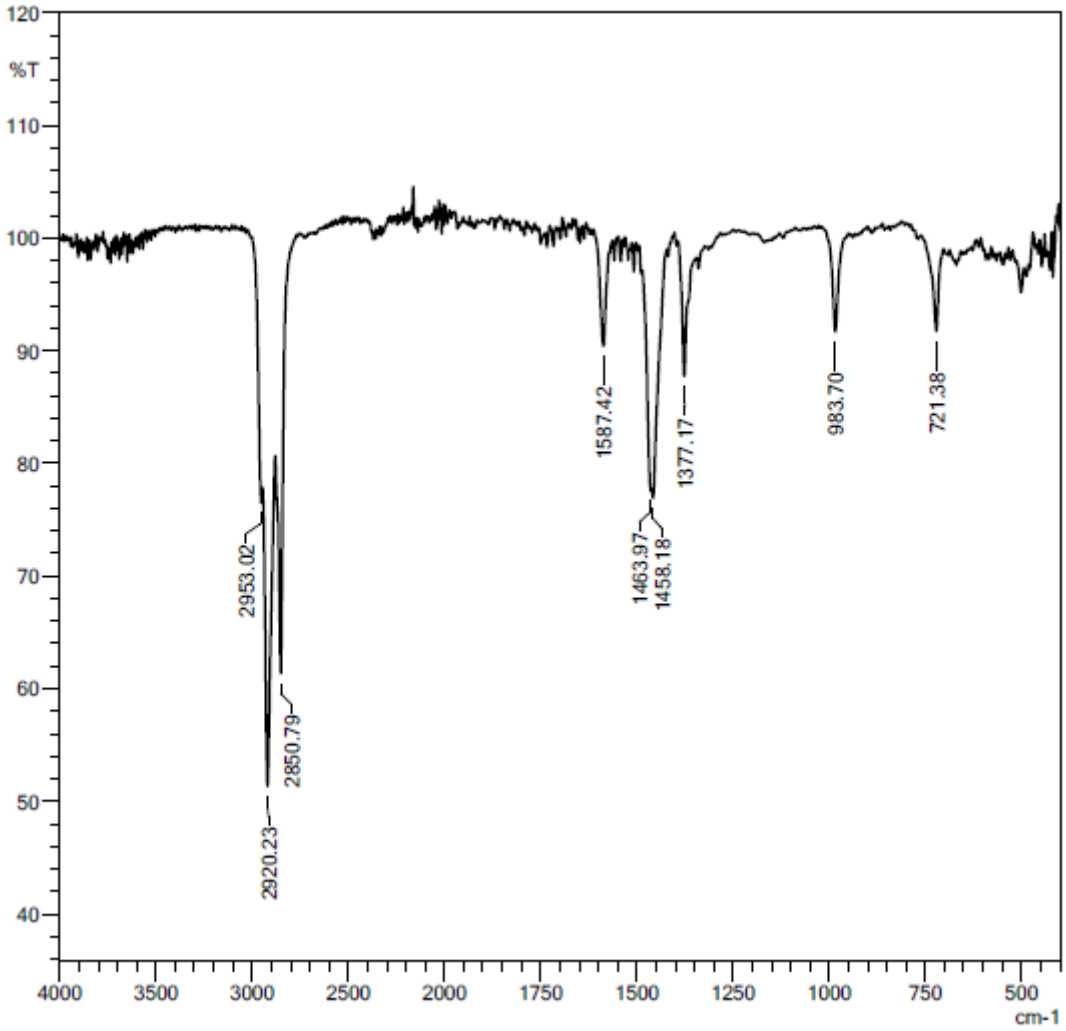

Figure 20: FTIR graph for lipogels formed with 8% aluminum stearate when analyzed after one week

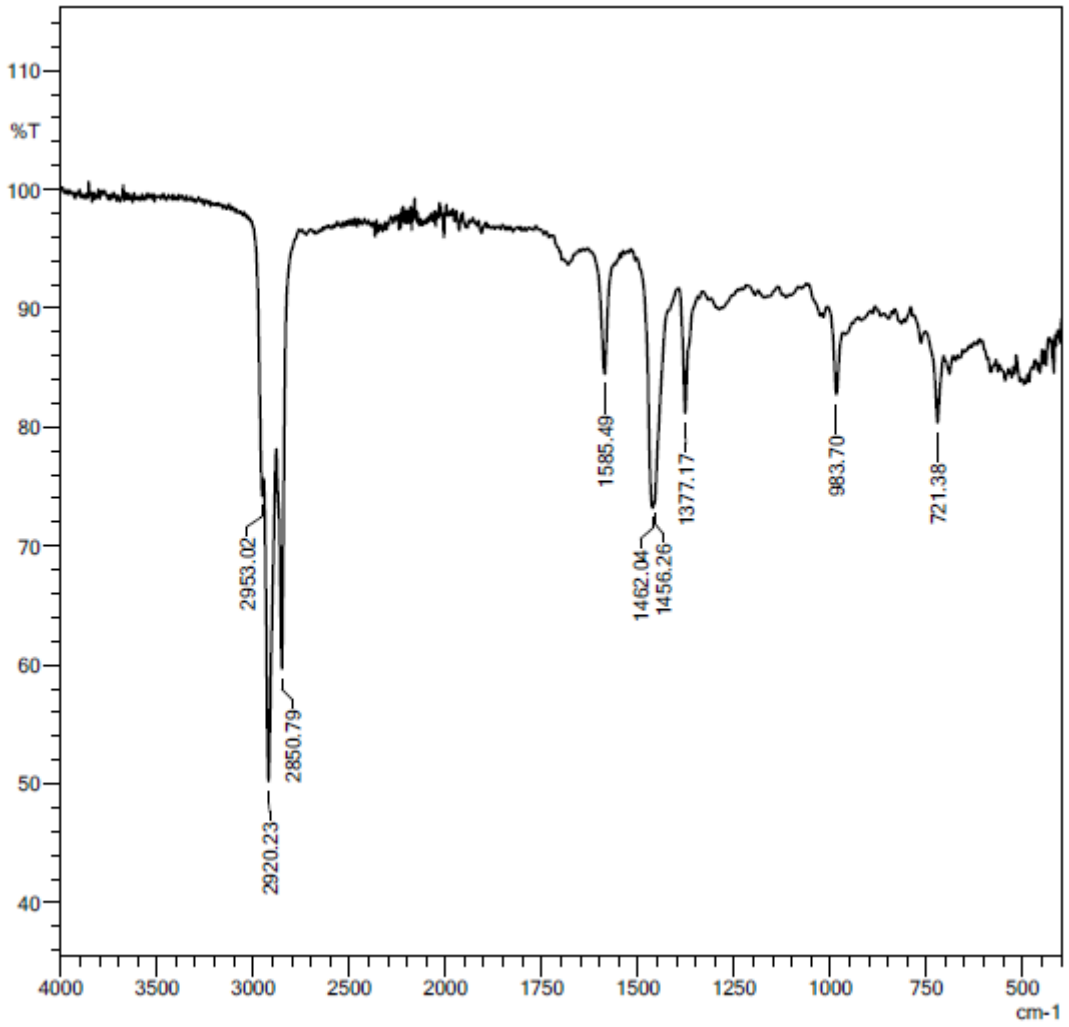

Figure 21: FTIR graph for lipogels formed with 9% aluminum stearate when analyzed after one week

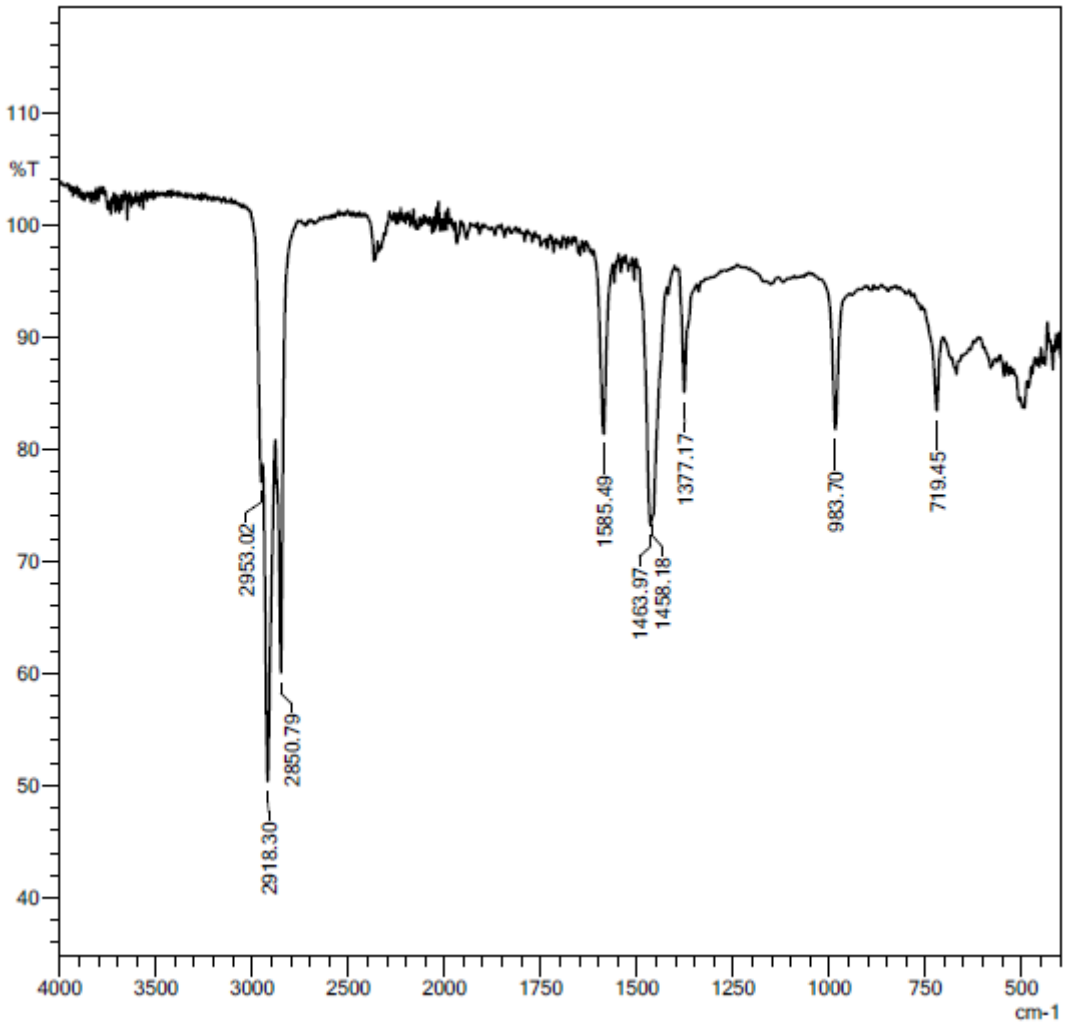

Figure 22: FTIR graph for lipogels formed with 10% aluminum stearate when analyzed after one week

Appendix B: DSC of Prepared Lipogels

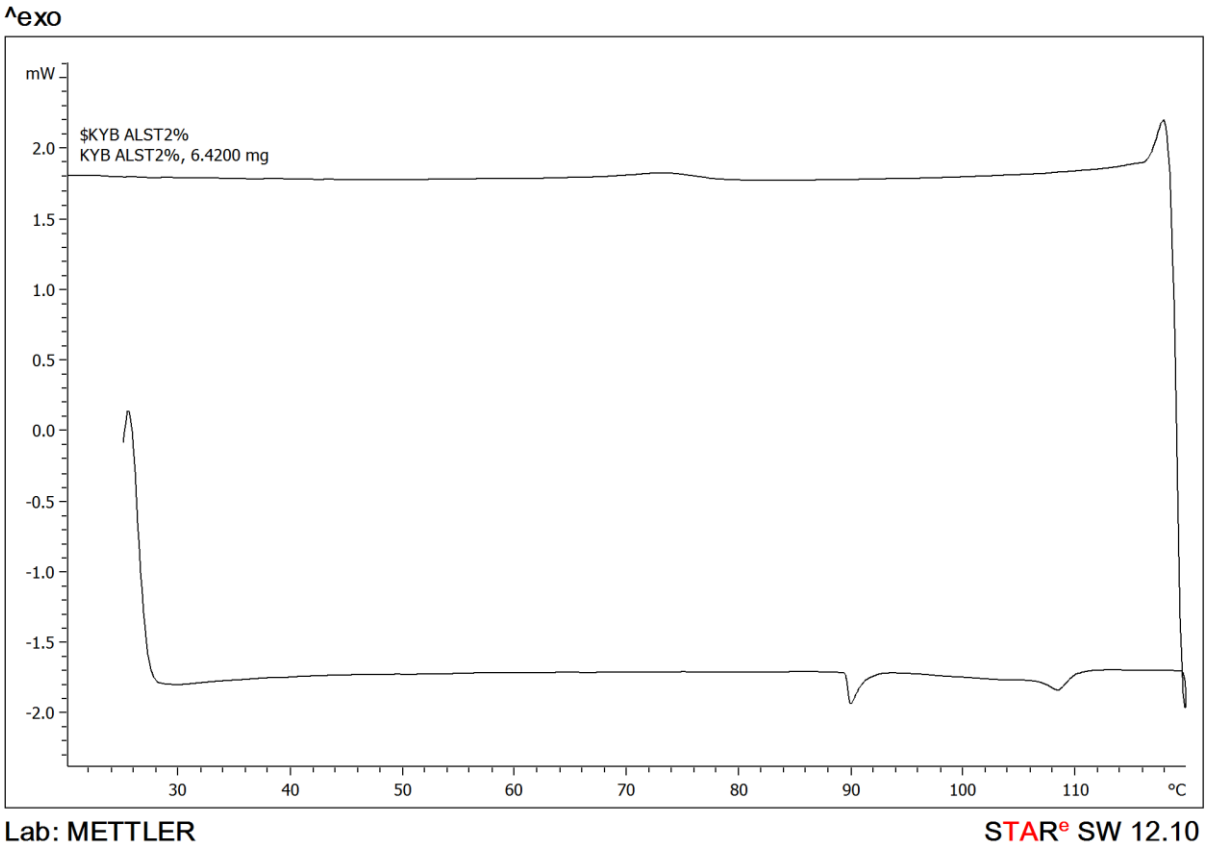

Figure 23: DSC graph for the lipogels formed with 2% aluminum stearate

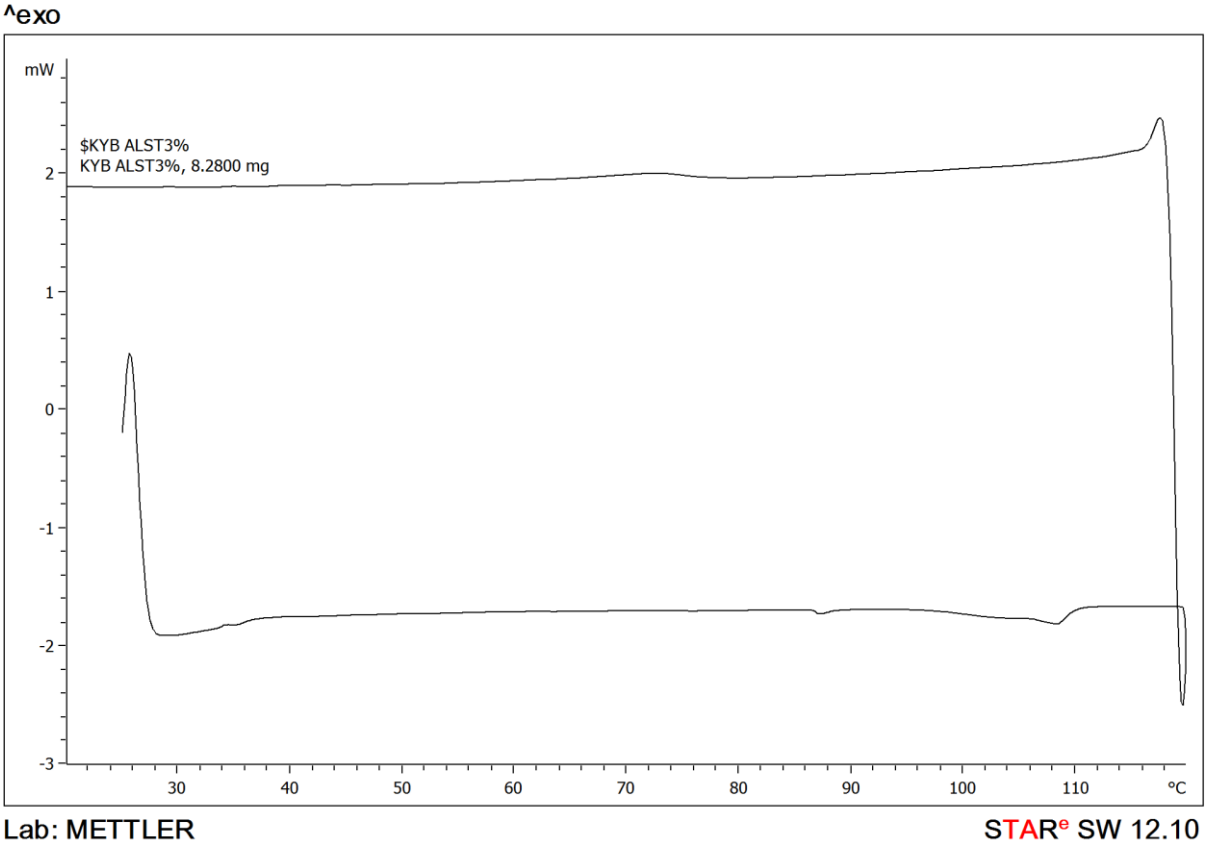

Figure 24: DSC graph for the lipogels formed with 3% aluminum stearate

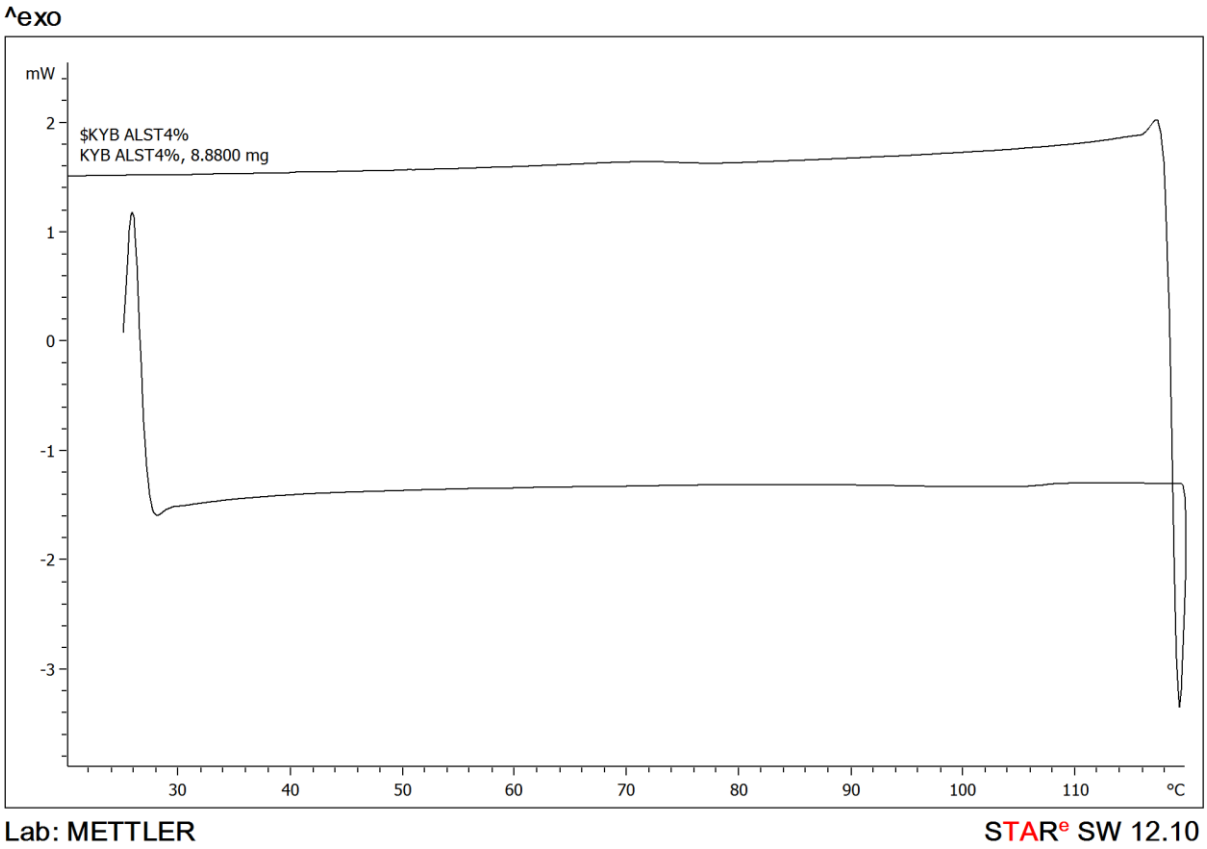

Figure 25: DSC graph for the lipogels formed with 4% aluminum stearate

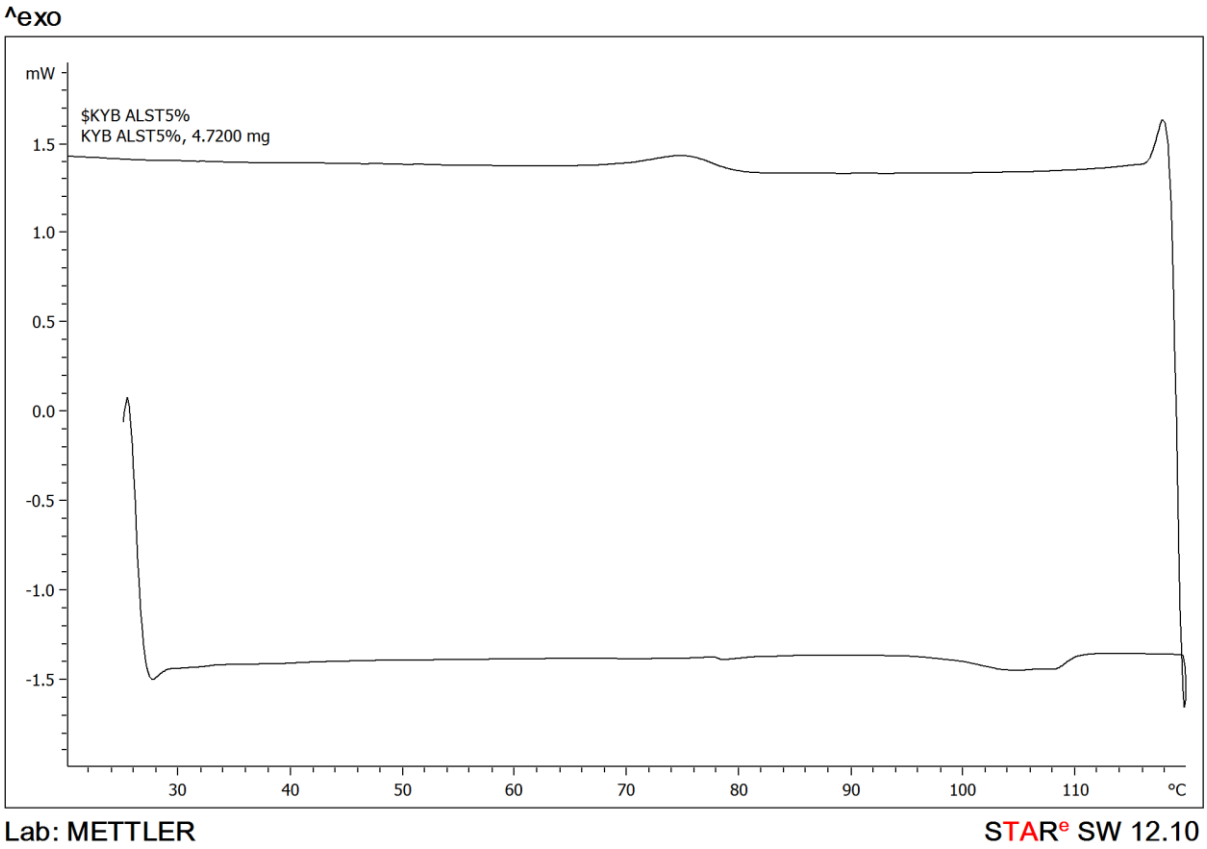

Figure 26: DSC graph for the lipogels formed with 5% aluminum stearate

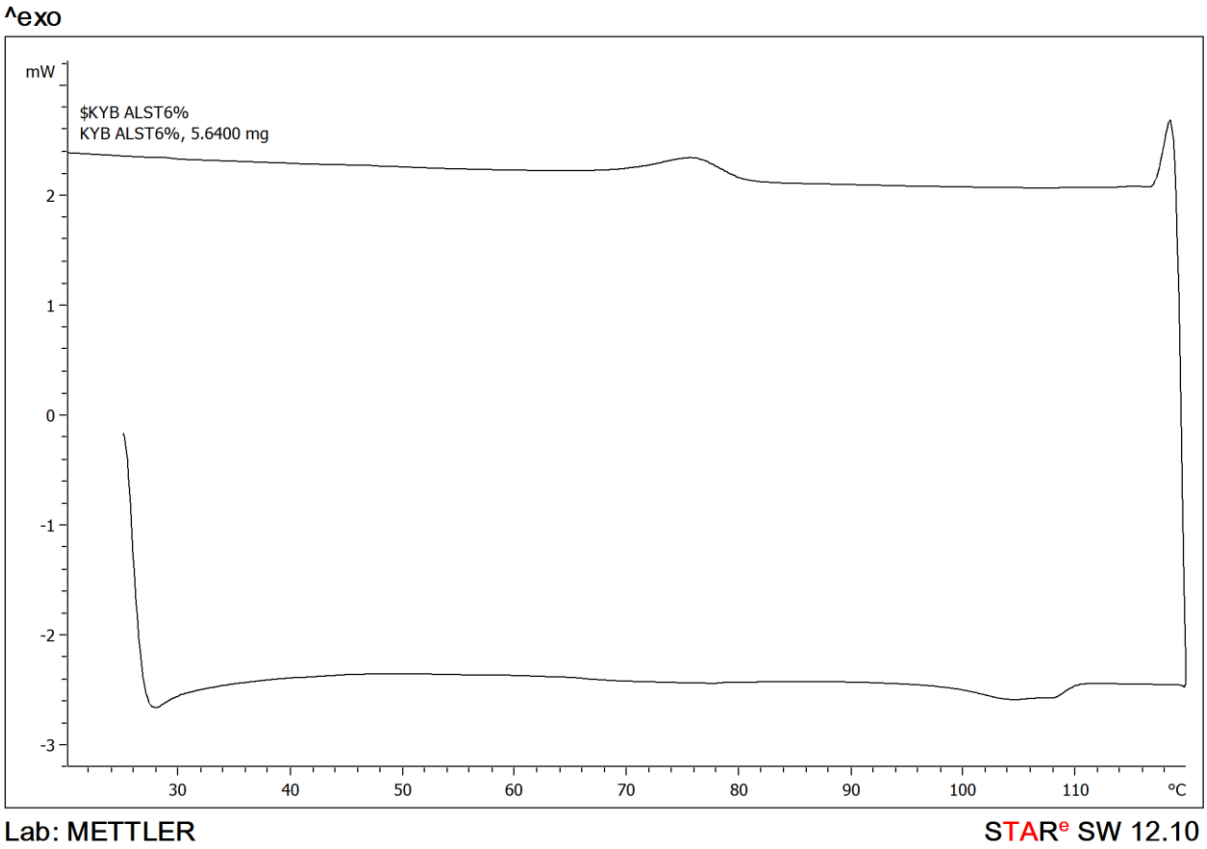

Figure 27: DSC graph for the lipogels formed with 6% aluminum stearate

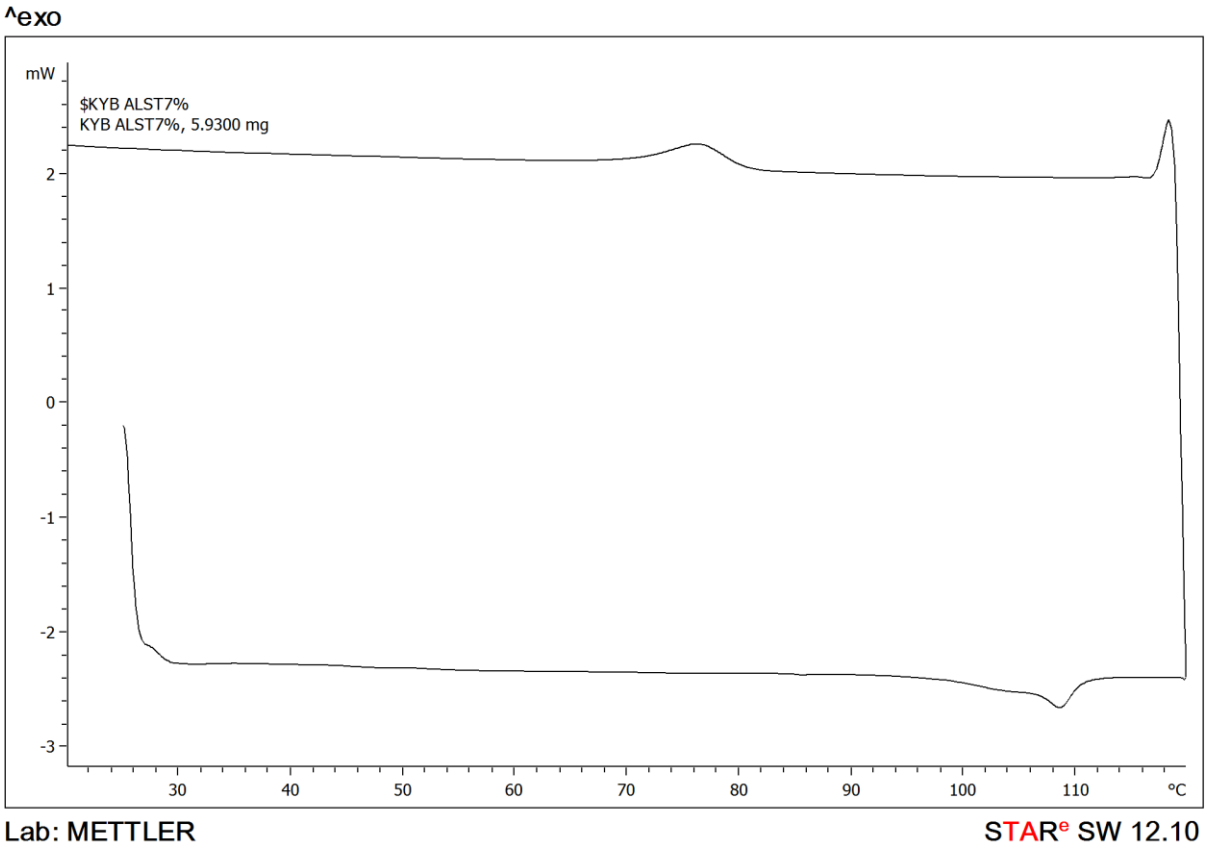

Figure 28: DSC graph for the lipogels formed with 7% aluminum stearate

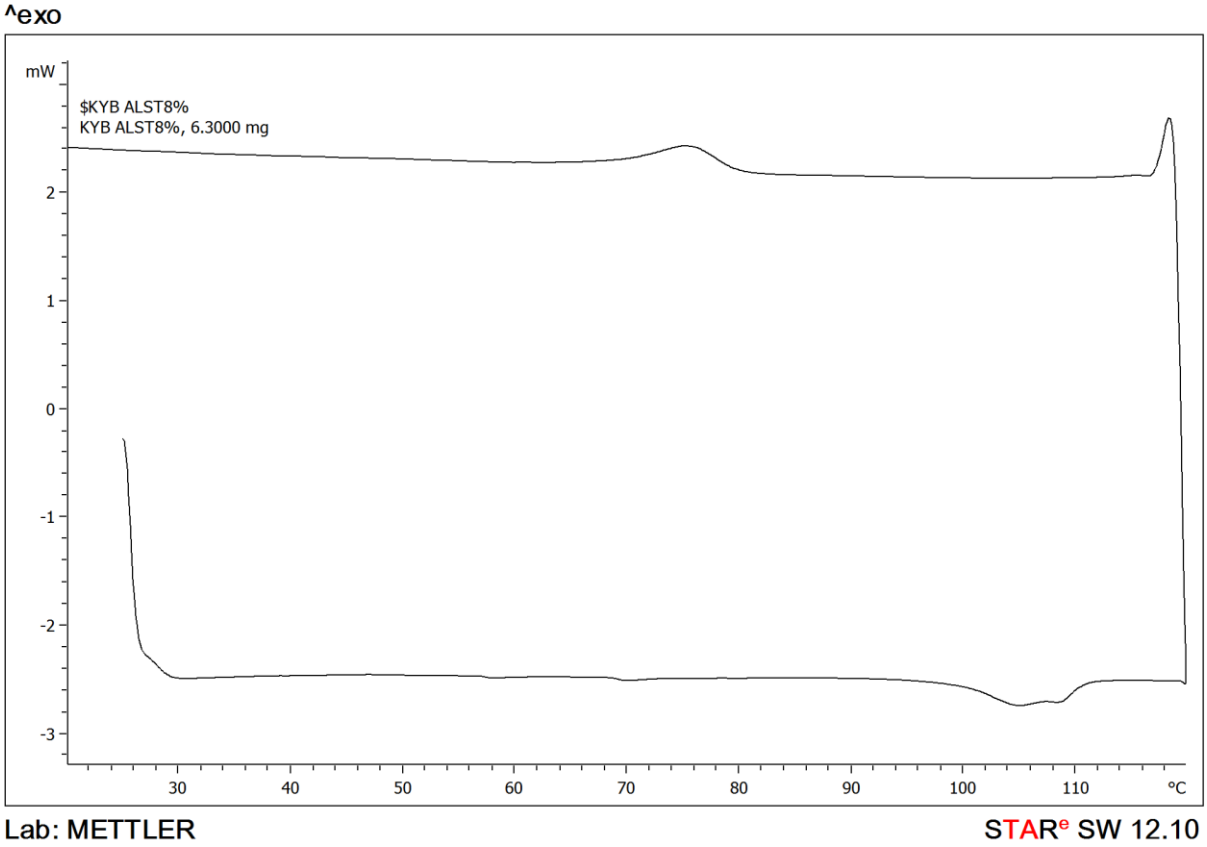

Figure 29: DSC graph for the lipogels formed with 8% aluminum stearate

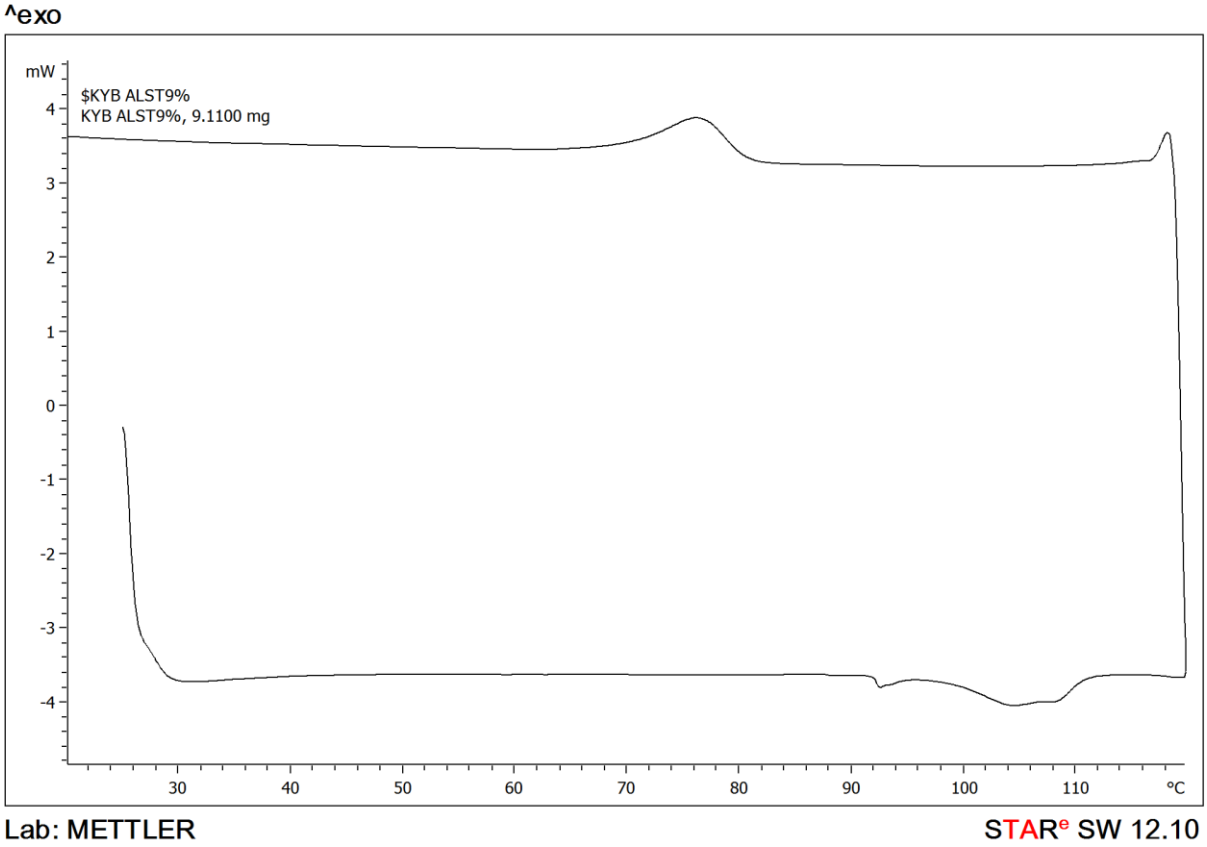

Figure 30: DSC graph for the lipogels formed with 9% aluminum stearate

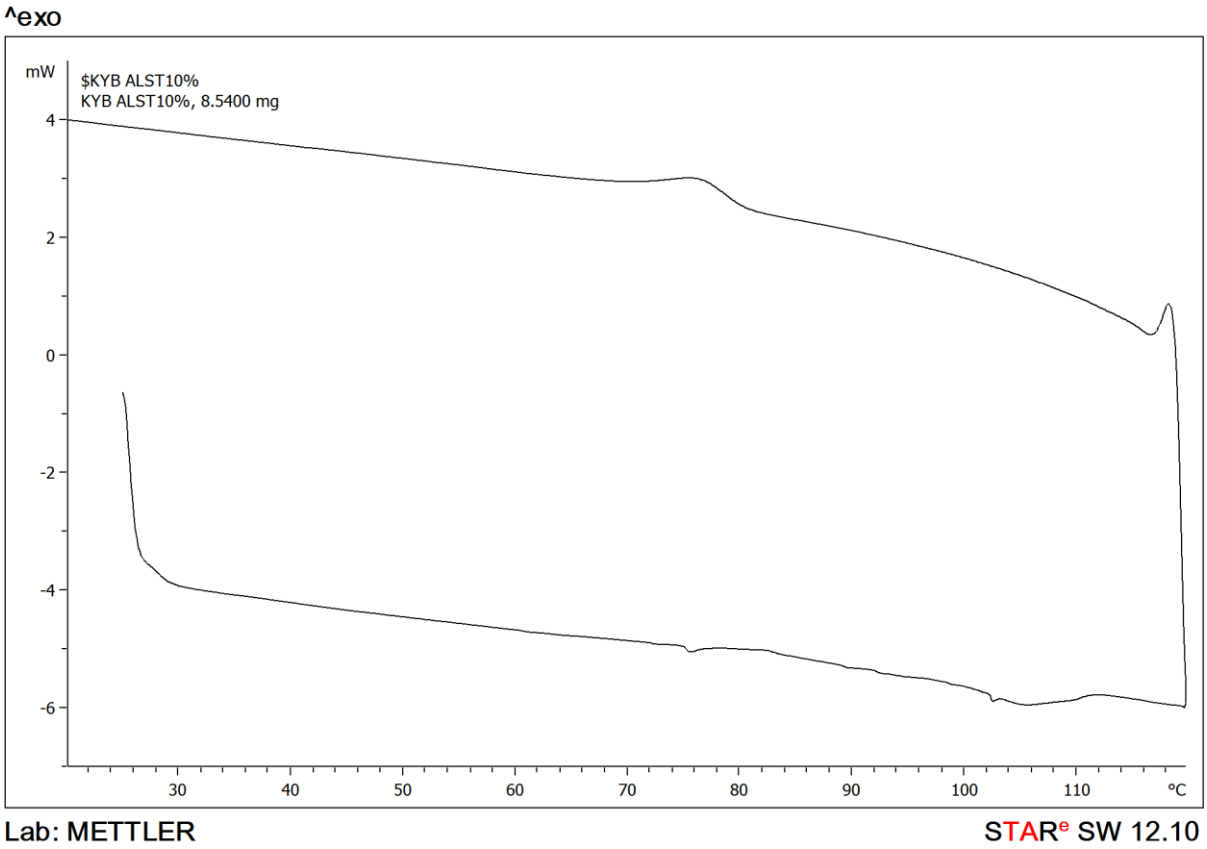

Figure 31: DSC graph for the lipogels formed with 10% aluminum stearate