REVIEW   **Open Access**

Evaluation of physical and chemical stability of semisolid preparations towards beyond-use date

Dyani Primasari Sukamdi[ID]*, Zulfa Sekar Dewinda, Vella Lailli Damarwati[ID], Nurul Maziyyah[ID], Dhecella Winy Cintya Ningrum

ABSTRACT

Background: Semi-solid formulations require careful consideration due to potential drug interactions and incompatibilities. The stability of these compounds is crucial for determining the quality of a preparation, often assessed by its designated shelf life.

Objective: This research synthesizes previous studies to provide a comprehensive assessment of the quality and stability of semi-solid drugs, focusing on evaluating their physical and chemical stability in relation to the Beyond Use Date (BUD).

Methods: A literature review was conducted using the Google Scholar database, yielding eight articles that met the established inclusion and exclusion criteria and were pertinent to the research topic.

Results: The evaluations of physical stability indicated that preparations are stable when stored under standard conditions, away from light, and when formulated with suitable bases. The chemical stability assessments revealed a decline in potency or concentration at elevated temperatures.

Conclusion: The study concludes that, within the parameters of stability evaluated, semi-solid drug preparations remain viable for use.

Keywords: semi-solid formulations, drug stability, Beyond Use Date (BUD), pharmaceutical quality, chemical and physical stability

Introduction

The preparation of drugs can involve compounding or manufacturing by the pharmaceutical industry [1]. Compounding medicine is often required due to the limited variety of commercially available drugs [2]. Drug compounding allows for customization of doses to meet patient requirements, improving the ease and effectiveness of medication administration for patients with unique health needs [3]. However, the drug compounding requires careful attention to avoid drug interactions, incompatibility, or issues with the miscibility of drugs and excipients or their containers, which can lead to reduced drug efficacy and alterations in dosage forms [2].

Pharmacists play a crucial role in ensuring the quality of these preparations, maintaining the safety and stability of compounded medications. The stability, a crucial aspect of preparation quality [4], is primarily determined by the assigned beyond use date (BUD). Accuracy is needed in deciding the BUD for formula drug preparations because formulated drugs have different physical and chemical characteristics according to each ingredient [5]. Medications that are used past their BUD may not only fail to achieve their intended therapeutic effects but also pose risks to patient health. Additionally, semisolid topical preparations, commonly prescribed and utilized for external medicinal or dermatological purposes, constitute a significant portion of compounding medications. Given their prevalence, it is vital to conduct thorough study to assess the stability

Department of Pharmacy, Faculty of Medical and Health Sciences, Universitas Muhammadiyah Yogyakarta, Jl. Brawijaya, Tamantirto, Kasihan, Bantul, Daerah Istimewa Yogyakarta 55183, Indonesia

*Corresponding author: Jl. Brawijaya, Tamantirto, Kasihan, Bantul, Daerah Istimewa Yogyakarta 55183, Indonesia. E-mail: dyani.primasaris@umy.ac.id
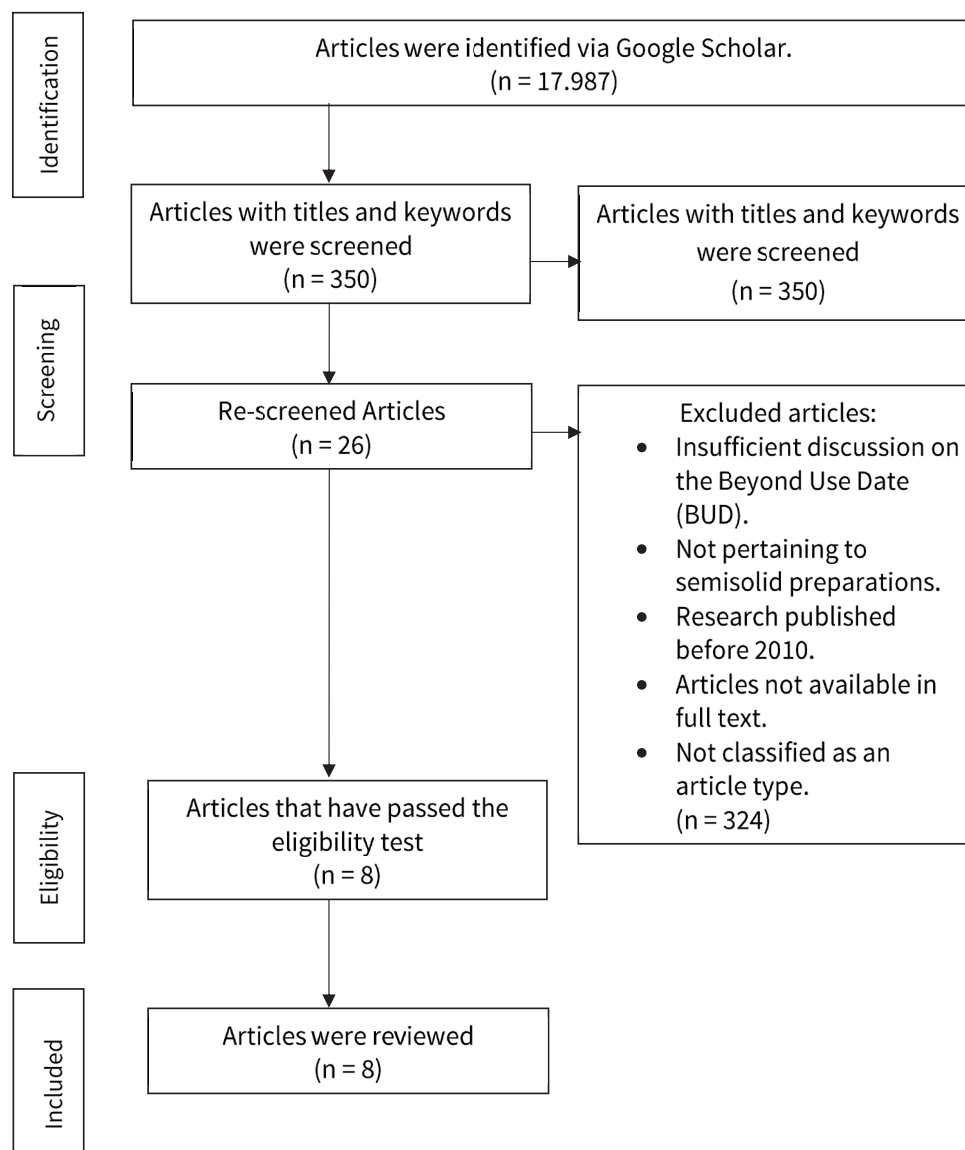
Figure 1. Article compilation algorithm

of these preparations in relation to their BUD, with a particular focus on semisolid forms.

Methods

This study employs a narrative review method, which involves collecting, selecting, reviewing, summarizing, and critically evaluating existing literature on the topic from various sources, including scientific articles, textbooks, conference proceedings, and other report documents.

The inclusion criteria for literature were research or original articles focusing on evaluating the physical and chemical stability of semisolid formulations, the impact of this stability, and the determination of the beyond

use date (BUD). These articles must be available in full text and published within the timeframe of 2010 to 2020. Exclusion criteria were set for articles published before 2010, those not available in full text (i.e., only abstracts are available), and articles not related to semisolid formulations.

The article search was conducted using the Google Scholar database, using a specific set of keywords related to this research. These keywords included "stability," "topical prescription drug," "pharmaceutical compounding," "semisolid compounded preparation," "use period," "beyond use date," "pharmaceutical compounding," "semisolid," and "physical and chemical stability." The process of searching for articles is depicted in Figure 1.

Table 1. Summary of data in the article

Article number	Author and year	Country	Stability test		Semisolid type	Testing time intervals	Results
			Physical	Chemistry			
1.	Khokhlova (2018)	Ukraine	✓	✓	Ointment	Day 0, 14, 30 and 60	The preparations remain appropriate for use for up to 2 months
2.	Gautam (2017)	USA	✓	✓	Cream	Day 7, 14, 28, 45, 60, 90, and 180	The preparations remain appropriate for use for up to 6 months
3.	Makeen (2018)	Arab Saudi	✓	✓	Ointment	Day 0, 30, 60, 90, and 120	The preparations remain appropriate for use for up to 4 months
4.	Basusarkar (2011)	USA	-	✓	Cream	N/A	The preparations remain appropriate for use for up to 3 months
5.	Basu Sarkar (2011)	USA	-	✓	Cream	Day 0, 30, and 60	The preparations remain appropriate for use for up to 2 months
6.	Nornoo (2016)	USA	✓	✓	Cream	- Day 0, 1, 7, 14, 21, 60, 90, dan 180 (organoleptic test, concentration, and pH) - Day 0, 28, 60, 90, and 180 (rheology test).	The preparations remain appropriate for use for up to 1 months
7.	Friciu (2016)	Canada	✓	✓	Ointment and cream	Day 0, 1 month, 2 months, 3 months, 6 months, dan 12 months (organoleptic test)	The preparations remain appropriate for use for up to 2 months
8.	Shakshuki (2019)	USA	✓	✓	Cream and gel	Day 0, 14, 28, dan 90	The preparations remain appropriate for use for up to 2 months

Initially, 17,987 articles were identified through this search. After applying the inclusion and exclusion criteria, 17,637 articles were excluded for not aligning with the selected keywords: (i) The first step involved keywords such as "stability," "topical prescription drug," "pharmaceutical compounding," "semisolid compounded preparation," "use period," and "beyond use date." (ii) In the second step, the focus was narrowed down to "pharmaceutical compounding," "semisolid," and "beyond use date." (iii) The third step refined the search further with keywords combined as follows: (stability) AND (physical and chemical stability) AND (topical OR semisolid compounded preparations) AND (beyond use date OR use period).

Following this keyword-based screening, articles with relevant titles were re-evaluated, resulting in 26 reports that satisfied the inclusion criteria. Subsequently, an eligibility test was performed on these reports, and 8 articles that passed this test were selected for review in this study.

Results

In this study, eight articles were reviewed that discussed semisolid preparations used for antifungal, anti-inflammatory, and pain relief therapies, employing either single active ingredients or their combinations. Out of these, six articles conducted both physical and chemical stability tests, whereas the remaining two focused solely on chemical stability assessments. The research on the physical and chemical stability of semisolid preparations in Indonesia is scarce, leading to reliance on seven articles from various international publications for this study. All articles undertook scientific investigations into the physical and chemical stability of these preparations (Table 1).

The physical stability evaluations reported in the articles encompassed organoleptic tests (examining appearance, color, odor, consistency, and texture), pH measurements, and viscosity assessments. These physical stability tests were detailed in articles 1, 2, 3, 6, 7, and 8. In contrast, articles 4 and 5 exclusively addressed

chemical stability. This study discusses the importance of stability studies in determining the appropriate packaging and storage conditions for drug products to prevent physical and chemical alterations [7].

Physical stability test

Organoleptic test

Organoleptic evaluations from article 1 revealed that an ointment, when stored under four different conditions (5±3°C, 25±2°C, 25±2°C with light exposure, and 40±2°C), remained stable without any change in color, smell, or consistency for two months, provided it was shielded from light [8]. Article 2 observed that a cream mixture maintained its stability, including appearance and odor, throughout a six-month period. Its texture stayed homogeneous and was deemed still usable by the end of this period [9]. According to article 3, no significant alterations in the appearance and color of an ointment mixture were noted over a four-month test duration [10].

The study outlined in article 6 assessed the stability of six cream formulas with three different bases under five varied conditions, noting instability with increased temperature and storage duration [11]. Article 7's findings indicated that nifedipine 0.5% in Petrolatum, nitroglycerin 0.2% in Petrolatum, and hydrocortisone 2.5% in Petrolatum remained stable for 12 months when stored in opaque polypropylene containers at room temperature (25°C). However, 2.5% hydrocortisone in a cream base only sustained its stability for two months, undergoing hydrolysis when incorporated into a cream base [12]. Evaluation from article 8 of eight cream formulas prepared with three different bases and tested under three temperature conditions over three months showed increased instability with temperature rise and time. At 4°C, notable instability was observed with the formation of a "recrystallized" solid. The preparation remained stable until day 28 at room temperature. At 40°C, the consistency changed to a sandy paste and even separated [13].

These organoleptic tests underscore the impact of temperature, storage container, and light exposure on the shelf-life (Beyond Use Date) of semisolid formulations. According to the United States Pharmacopeia (USP) guidelines, the BUD for topical formulations containing water should not exceed 30 days, and for those without water, up to six months [14]. The collective findings from the reviewed articles suggest that semisolid formulations generally remain stable and usable within the prescribed limit when stored under appropriate conditions.

pH test

The pH test aimed to ensure the safety of the preparations by verifying that they would not cause skin irritation upon application. The pH profile serves as an indicator of the preparation's stability [15]. In article 2, the cream formulations were tested at various intervals (days 0, 7, 14, 28, 45, 60, 90, and 180), resulting in average pH values of 8.92 ± 0.3 and 8.83 ± 0.3, respectively. These results indicate a higher, more alkaline pH level than is typically considered safe for skin, which has an ideal pH range of 4.5 to 6.5.

Article 6 reported that the pH of the cream mixture ranged between 5 and 6 when stored at temperatures from 4°C to 37°C, decreasing to 4-5 at higher temperatures. The testing intervals for this article were days 0, 1, 7, 14, 21, 28, 60, 90, and 180 [11]. The findings from article 6 suggest that the pH level of the cream mixture remains within the skin-friendly pH range of 4.5 to 6.5, indicating suitability for topical use.

It is unclear whether the semisolid preparations discussed in articles 1, 3, 7, and 8 met the required pH criteria for skin compatibility.

Viscosity test

The viscosity tests were conducted only in the studies reported by articles 2 and 6. The studies mentioned in articles 1, 3, 7, and 8 did not include viscosity measurements, leaving the stability of the formulations' viscosity in these articles unexplored.

In article 2, the viscosity of formulation preparations based on RECURA was measured, resulting in average viscosities of 167.529 ± 28.481 cps and 186.778 ± 20.003 cps, respectively. These measurements were taken at intervals on testing days 0, 7, 14, 28, 45, 60, 90, and 180 [9]. The findings suggest a relatively stable viscosity over the observed period.

Article 6's findings indicated that the viscosity of cream mixtures based on LipoBase and LipoDerm increased with both rising temperature and extended storage time, whereas the viscosity decreased when the base was Pluronic Lecithin Organogel (PLO) [11]. The higher the viscosity value, the lower the possibility of separation in the preparation. An increase in the viscosity value indicates that the preparation is more stable so that the rate of deterioration decreases [16].

Chemical stability test

In article 1, chemical stability was assessed using thin-layer chromatography (TLC) for a formula comprising herbal components (Marigold and Arnica tinctures), focusing on two primary constituents: flavonoids and kalenduloside. During a two-month storage period, the flavonoid and kalenduloside profiles remained stable at temperatures of 5±3°C and 25±2°C, provided there was protection from light exposure. However, at 25±2°C with light exposure and at 40±2°C, the stability of these compounds was compromised, as evidenced by reduced intensity and absence in TLC after one month. This suggests that the preparation's potency can be preserved for up to two months if stored at room temperature away from light [8].

Gautam eta al. (2017) used high-performance liquid chromatography (HPLC) to determine the levels of miconazole (10%) and fluconazole (10%) in a RECURA base. Initial concentrations were found to be 100.8%±0.3% for miconazole and 99.30%±0.6% for fluconazole. After 180 days, concentrations adjusted to 108.0%±1.0% for miconazole and 106.2%±0.2% for fluconazole, indicating that the potencies of these preparations remained relatively stable over six months under room temperature conditions [9].

Makeen (2018) evaluated the chemical stability of a methyl salicylate ointment formulation using UV-Vis spectrophotometry. They found that the preparation maintains its stability for a maximum of four months when stored at 4°C [10].

Basusarkar (2011) assessed the chemical stability of diclofenac cream formulations using high-performance liquid chromatography (HPLC). The creams were formulated with two different bases, Poloxamer Lecithin Organogel (PLO) Medflow Premix™ and Poloxamer Lecithin Organogel (PLO) Medflow Premix 30™, and tested over three months [17]. The assays revealed that the diclofenac cream in each base showed minimal drug degradation (less than 10%) at both 4°C and 25°C, suggesting that the preparations retain their potency for up to three months.

Basu Sarkar (2011) investigated 2% hydrocortisone cream formulations based on VersaPro™ cream, with assays conducted using HPLC at 0, 30, and 60 days. Testing occurred at room temperature (25°C) and cold temperature (4°C). Results indicated that the cream's concentration remained stable compared to day 0, under varying storage conditions. This stability infers that the cream's effectiveness is maintained for up to two months [18].

Nornoo (2016) examined ketoprofen formulas for chemical stability using HPLC. The formulas were incorporated into three different bases and subjected to five different storage temperatures (4°C, 25°C, 37°C, 45°C, and 65°C) for six months. The calculated shelf life (t90%)—the time during which the drug remains above 90% of its initial concentration—was 85.9 days for preparations in LipoDerm and 109.94 days in LipoBase, significantly outlasting the PLO base, which had a shelf life of only 44.81 days at 25°C. The degradation rate, which accelerates with increased storage temperature, affected shelf life negatively. Additionally, storage beyond 90 days was found to compromise the physical and chemical stability of ketoprofen cream. Therefore, the effective lifespan of ketoprofen preparations in LipoDerm and LipoBase is approximately two months, while those in PLO base are viable for about one month [11].

Hydrocortisone, nifedipine, and nitroglycerin formulations were assessed by Friciu (2016) for chemical stability using high-performance liquid chromatography (HPLC) over 12 months at 25°C. The mixtures containing 0.5% nifedipine, 0.2% nitroglycerin, and 2.5% hydrocortisone in petrolatum exhibited relative stability, maintaining at least 90% of their initial concentrations throughout the testing period. In contrast, the 2.5% hydrocortisone formula in a cream base showed instability, dropping to 88.7% after three months and 81.8% after six months. The findings suggest that the mixed formula of nifedipine, nitroglycerin, and hydrocortisone in petrolatum, when stored in opaque polypropylene containers, retains its efficacy for up to 12 months, while the 2.5% hydrocortisone in a cream base remains stable for only up to 2 months [12].

Shakshuki (2019) assessed the 10% gabapentin formula for chemical stability, formulated in LipoDerm Cream, Versa Base Gel, and Emollient Cream, and stored at temperatures of 4°C, 25°C, and 40°C for 90 days. Gabapentin in LipoDerm Cream showed a significant increase in concentration at 25°C and 40°C after 28 and 90 days, whereas at 4°C, the concentration remained unchanged. The Versa Base Gel and Emollient Cream bases experienced no significant changes in concentration, though levels tended to increase over the 90 days, especially at 40°C. The results indicate that the gabapentin preparation's effectiveness is best maintained for no longer than one month [13].

Conclusion

The findings from the physical stability evaluation indicate that the preparation remains stable when stored at moderate temperatures, shielded from light, and formulated with the appropriate base. The chemical stability assessment revealed a reduction in potency or concentration at elevated temperatures. Overall, the stability evaluation suggests that the formulation remains viable for use.

Acknowledgment

Conflict of Interest

No potential conflicts of interest were reported by the authors.

Author contributions

DPS plays a role in drafting concepts, leading research, and compiling publication texts. ZFD and DPS collect data, review articles and discuss research results. VLD and NM contributed to designing research concepts, improving authorship, and providing suggestions regarding research data analysis. ZFD and DWC compiled and wrote the publication text.

References

1. Betha OS, Yardi Y, Alvionita Y, Zilhadia Z, Siregar BJ. (2019). Mutu Sediaan Racikan Puyer di Kecamatan Ciputat Timur. Pharm Biomed Sci J, 1(1), 21-28. https://doi.org/10.15408/pbsj.v1i1.12765

2. Rochjana AUH, Jufri M, Andrajati R, Sartika RAD. (2019). Masalah Farmasetika dan Interaksi Obat pada Resep Racikan Pasien Pediatri: Studi Retrospektif pada Salah Satu Rumah Sakit di Kabupaten Bogor. Indones J Clin Pharm, 8(1), https://doi.org/10.15416/ijcp.2019.8.1.42

3. Widyaswari R, Wiedyaningsih C. (2017). Evaluasi Profil Peresepan Obat Racikan Dan Ketersediaan Formula Obat untuk Anak Di Puskesmas Propinsi DIY. Maj Farm, 8(3), 227-234. https://journal.ugm.ac.id/majalahfarmaseutik/article/view/24079/15756.

4. K Mohiuddin A. (2020). Extemporaneous compounding: Cautions, controversies and convenience. IP Int J Compr Adv Pharmacol, 3(4),124-137. https://doi.org/10.18231/2456-9542.2018.0028

5. Herawati F, Surabaya U. (2012). Beyond Use Date. Bul Rasional, 10 (3),16-24.

6. Kristina SA, Wiedyaningsih C, Widyakusuma NN, Aditama H. (2017). Extemporaneous Compounding Practice By Pharmacists: a Systematic Review. Int J Pharm Pharm Sci, 9(2), 42. https://doi.org/10.22159/ijpps.2017v9i2.15681

7. Iqbal A, Muhammad AS, Sofia A. (2016). Stability of Drugs and Drug Products, Vol 23.

8. Khokhlova KO ZO. (2018). Investigation of the Physical, Chemical, and Microbiological Stability of Oral Solutions Compounded with Herbals. Int J Pharm Compd, 22(3), 240-246.

9. Gautam P, Light B, Purvis T. (2017). Stability of Two Antifungal Agents, Fluconazole and Miconazole, Compounded in HUMCO RECURA Topical Cream to Determine Beyond-Use Date. Int J Pharm Compd, 21(2), 154-159.

10. Makeen H, Pancholi S, Alhazmi H, et al. (2018). Stability Testing of Extemporaneous Preparation of Methyl Salicylate Ointment Makeen. J Heal Spec, 6, 72-6. doi:10.4103/jhs.JHS_14_18 https://doi.org/10.4103/jhs.JHS_14_18

11. Nornoo AO, Wulz J, Yoon H, Nan Y, Lese M. (2016). Impact of the chemical and physical stability of ketoprofen compounded in various pharmaceutical bases on its topical and transdermal delivery. Pharm Dev Technol, 21(2), 204-213. https://doi.org/10.3109/10837450.2014.986684

12. Friciu M, Chefson A, Leclair G. (2016). Stability of hydrocortisone, nifedipine, and nitroglycerine compounded preparations for the treatment of anorectal conditions. Can J Hosp Pharm, 69(4), 329-333. https://doi.org/10.4212/cjhp.v69i4.1578

13. Shakshuki A, Yeung P, Agu RU. (2019). Compounded gabapentin for neuropathic pain: Stability and beyond-use date (BUD) in some commonly used bases. J Am Pharm Assoc, 59(4), 514-520. https://doi.org/10.1016/j.japh.2019.02.012

14. USP. (2014). ⟨795⟩ Pharmaceutical Compounding-Nonsterile Preparations. Revis Bull.

15. Susilowati EP, Wahyuningsih SS. (2014). Optimasi Sediaan Salep Yang Mengandung Eugenol Dari Isolasi Minyak Cengkeh (Eugenia caryophylatta Thunb.). Indones J Med Sci,1(2), 29-34.

16. Husni P, Hisprastin Y, Januarti M. (2019). Formulasi Dan Uji Stabilitas Fisik Sediaan Emulsi Minyak Ikan Lemuru (Sardinella lemuru). J Ilm As-Syifaa, 11(2), 137-146. https://doi.org/10.33096/jifa.v11i2.575

17. Basu Sarkar A, Sekar C. (2011). Stability Studies on Diclofenac Sodium Cream. Int J Adv Pharm Anal, 1(1), 3-6. https://doi.org/10.7439/ijapa.v1i1.3

18. Sarkar AB, Dudley R, Melethil S, Speidel J, Bhatt GM. (2011). Chemical Stability of Hydrocortisone in Topical Preparation in Proprietary VersaProTM Cream Base. Inov Pharm, 2(3). https://doi.org/10.24926/iip.v2i3.237