Sustained-Release Hydrogel Formulation for Gabapentin Delivery in Neuropathic Pain Management

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KEYWORDS

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Abstract

Neuropathic pain is a chronic, complex disorder that significantly affects a patient's quality of life and is typically treatment refractory of conventional treatments such as opioids and NSAIDs. Gabapentin is an efficacy in treating neuropathic pain, particularly in diabetic neuropathy and post herpetic neuralgia as a GABA analogue. However, this has limitation due to its low bioavailability, short half life, and associated adverse effects, which render consistent therapeutic outcome challenging. To overcome these limitations, promising sustained release formulations especially based on hydrogels are available. Biocompatible, high drug loading systems that offer sustained release, hydro-gels are an improvement to patient compliance and therapeutic efficacy. In this work we explore the possibility of using hydrogel based drug delivery systems for the treatment of neuropathic pain upon administering Gabapentin with research on existing hydrogel formulations and their advantages over traditional delivery methods. Formulation optimization and clinical applicability are also discussed, and additional research will be necessary before this approach can be developed into a commercially competitive technology.

1. Introduction

Neuropathic pain is a complex, chronic neuropathic process. Unlike nociceptive (tissue injury) pain, neuropathic (pain from abnormal sensory information processing in the peripheral and central nervous system) pain presents not from the tissue itself but from paint as a sensation (e.g., burning, tingling, stabbing). Diabetic neuropathy, post herpetic neuralgia, spinal cord injury and multiple sclerosis are common causes of neuropathic pain (Boulton et al., 2005; Jensen et al., 2011). Millions are affected globally by neuropathic pain that is associated with substantial impairment in quality of life and productivity (Vos et al., 2015). Neuropathic pain is still a syndrome with few effective analgesics, and despite the challenge these represent, traditional analgesics, such as opioids and NSAIDs, and steroid medications are either ineffective or have extensive side effects (Finnerup et al., 2015). Consequently, there has been intensive scrutiny of alternative therapies, including anticonvulsants and antidepressants. The most widely prescribed neuropathic pain drugs, such as gabapentin, are analogues of the gamma aminobutyric acid (GABA) and show much efficacy in treating conditions like diabetic neuropathy and postherpetic neuralgia (Dworkin et al., 2003). Binding of gabapentin to the α2δ subunit of voltage gated calcium channels reduces the release of excitatory neurotransmitters that transmit pain (Gee et al., 1996).

Although Gabapentin is clinically successful, though, it suffers from major drawbacks. It has relatively low bioavailability (approximately 30%), short half life (5–7 hours) and, consequently, requires frequent dosing to maintain therapeutic levels (Baker et al., 2004). Fluctuating plasma concentrations and suboptimal therapeutic outcomes result primarily from these pharmacokinetic limitations (Ziegler et al., 2002). It further complicates Gabapentin's clinical use because higher doses can also produce side effects including dizziness, ataxia, and fatigue (Buchheit et al., 2011). As a solution, researchers are working on the formulation of sustained release Gabapentin with improved pharmacokinetic profile and a decreased dosing frequency and increased patient compliance (O'Connor and Dworkin 2009). One potential solution to these problems, hydrogels, a network of hydrophilic polymers that are three dimensional in structure, have emerged in drug delivery systems as a biocompatible, high drug loading capacity, controlled release delivery technique (Peppas et al., 2000). The potential of sustained release hydrogel formulations for Gabapentin delivery is explored in this paper, which discusses the potential use of these systems as an adjunctive therapy for the management of neuropathic pain.

2. Literature Review

2.1 Gabapentin and Its Use in Neuropathic Pain

However, Gabapentin also has proven benefit in management of neuropathic pain in clinical trials (Dworkin et al., 2003). By binding to the α2δ subunit of voltage-gated calcium channels, gabapentin exerts its analgesic effects by inhibiting the release of such excitatory neurotransmitters as glutamate and substance P and thereby decreasing neuronal excitability and changing the pain signaling pathways (Gee et al., 1996). Unlike many therapeutics that can exacerbate abnormal nerve activity and increase pain (Boulton et al., 2005), this mechanism of action is particularly effective in those conditions such as diabetic neuropathy and post herpetic neuralgia where abnormal nerve activity contributes to pain. Despite its therapeutic success, pharmacokinetics of Gabapentin pose challenge in clinical practice. The bioavailability of the drug is nonlinear and falls with increasing dose. Even at high doses of Gabapentin only approximately 30-60% of the drug is absorbed and plasma concentrations do not increase linearly (Baker et al., 2004). Frequent dosing is necessary to reach therapeutic plasma levels, necessitating patient adherence that can lead to patient variability of drug concentrations which may then impede consistency of treatment outcomes (Ziegler et al., 2002).

2.2 Hydrogel-based Drug Delivery Systems

Three dimensional polymer networks that retain large amounts of water have proven to be highly effective in controlled drug delivery applications (Peppas et al., 2000). A favored type of sustained release drug delivery systems has been those constituted by their biocompatibility, capacity of encapsulating a variety drugs, controlled release properties. Various mechanisms of drug release mediate the release of drugs from hydrogels: diffusion, swelling and degradation, and hydrogels can be engineered to release drugs over extended periods (Santoro et al. 2014). With adjustment of the chemical composition, crosslinking density and hydrophilicity of the hydrogel matrix, release rate of drug can be tuned to desired therapeutic outcomes (Buwalda et al., 2017). Natural or synthetic, hydrogels can be divided into two categories. However, natural hydrogels such as alginate, chitosan, or gelatin, suffer from poor mechanical strength, while being more biocompatible (Chung et al., 2017). In contrast, synthetic hydrogels such as polyacrylamide and poly (lactic acid) can be designed to display certain release profiles but are questionable in terms of their toxicity (Kushwaha et al., 2017). Due to their ability to maintain stable drug release over extended periods, polymeric hydrogels represent a promising delivery system for Gabapentin; they may improve the therapeutic profile of Gabapentin and increase patient adherence to the prescribed treatment regimen.

2.3 Sustained-Release Systems for Gabapentin

Several studies have been conducted with sustainable release of Gabapentin in order to improve its therapeutic efficacy and reduce the side effects therewith. The drug release profile has also been improved using traditional approaches of polymeric matrices or liposomal encapsulation. Unfortunately, though, these systems tend to have release problems, non-uniform release and stability issues, which can result in poor clinical results (Rahman et al., 2018). In contrast, hydrogel systems have demonstrated superior release performance because they possess a high water content, and therefore swell in response to biological fluids, resulting in more predictable and controlled release profiles (Choi et al., 2012). Moreover, biodegradable hydrogels can be fabricated for hydrogel drug delivery systems to alleviate the problem of surgical removal after drug release (Gao et al., 2016).

2.4 Previous Research on Hydrogel Formulations of Gabapentin

Several of these studies have explored hydrogel formulations for controlled release of Gabapentin. An example of these materials includes polymeric hydrogels comprising polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC) tested for their ability to release Gabapentin over 24–48 hours, achieving therapeutic plasma levels while diminishing the risk of side effects (Sharma et al., 2015). Alginate based hydrogels polymerized from alginate family of anionic polymers have also been investigated, as these hydrogels not only encapsulate drugs, but can be degraded in a controlled manner, offering very long release profiles (Zhang et al., 2013). Although promising, stability and release rate optimization remains a challenge, particularly when scaling up these formulations for clinical use. Refinements of these systems are needed as well as improvements in their stability, as these systems are not at the ready for wide spread clinical application due to the manufacture concerns.

3. Methodology

3.1 Materials

- **Polymers**: Chitosan (Sigma-Aldrich, USA) and Polyvinyl Alcohol (PVA, Sigma-Aldrich, USA) were selected as the base polymers for the hydrogel matrix due to their biocompatibility and ability to form strong hydrogels.
- **Crosslinking Agent**: Tripolyphosphate (TPP) was used as the crosslinking agent for chitosan.
- **Gabapentin**: Gabapentin (Sigma-Aldrich, USA) was used as the active pharmaceutical ingredient for formulation. It was characterized for purity and content.
- **Solvents**: Distilled water and phosphate-buffered saline (PBS, pH 7.4) were used for formulation and release studies.
- **Other reagents**: Acetone, ethanol, and other solvents were used as required.

3.2 Preparation of Gabapentin-Loaded Hydrogel

1. **Hydrogel Preparation**:
    - **Chitosan-PVA Hydrogel Formation**: A **chitosan-PVA hydrogel** was prepared by dissolving chitosan in 1% (v/v) acetic acid solution (pH 4.5). PVA was dissolved in distilled water by heating at 90°C for 1 hour. Both solutions were mixed in varying ratios (e.g., 80:20, 70:30, 60:40) of chitosan to PVA to determine the optimal ratio for drug delivery.
    - **Incorporation of Gabapentin**: Gabapentin was dissolved in distilled water and added to the polymer blend. The final concentration of Gabapentin was optimized to ensure the correct drug loading (e.g., 10 mg per hydrogel sample).
2. **Crosslinking**: The hydrogel was crosslinked using tripolyphosphate (TPP) solution (1%, v/v). The crosslinking reaction occurred by adding the TPP solution dropwise to the polymer-Gabapentin mixture. The resultant hydrogel was allowed to form for 2 hours at room temperature.
3. **Lyophilization and Drying**: The formed hydrogel was lyophilized to obtain a dry, stable product. After lyophilization, the hydrogels were stored in a desiccator at room temperature for further use.

3.3 Characterization of the Hydrogels

1. **Swelling Behavior**: The swelling behavior of the hydrogel was evaluated by immersing the dried hydrogel samples (1 cm × 1 cm) in **simulated gastric fluid (SGF)** and **phosphate-buffered saline (PBS)** at 37°C. The swollen hydrogels were weighed at predetermined time intervals (e.g., 1, 2, 4, 6, 8, 12, 24 hours) to determine the percentage swelling index (SI) calculated by the formula:

$$\text{Swelling Index} = \frac{(W_t - W_0)}{W_0} \times 100$$

where W_t is the weight of the hydrogel at time t and $W_0$is the initial weight.

2. **Drug Loading and Encapsulation Efficiency**: The amount of Gabapentin encapsulated in the hydrogel was determined by dissolving the swollen hydrogel in PBS and analyzing the concentration of Gabapentin using **High Performance Liquid Chromatography (HPLC)**. The encapsulation efficiency (EE) was calculated as:

$$Encapsulation\,Efficiency\,(\%) = \frac{Amount\,of\,\,Gabapentin\,in\,Hydrogel}{Total\,\,Amount\,of\,\,Gabapentin\,\,Added} \times 100$$

3. **Drug Release Studies**: In vitro drug release was performed by immersing the hydrogels in **PBS (pH 7.4)** at 37°C. Samples were taken at regular intervals (e.g., 1, 2, 4, 8, 12, 24, and 48 hours) and the released Gabapentin concentration was determined using HPLC. The **cumulative drug release** was plotted against time.

4. **Fourier Transform Infrared (FTIR) Spectroscopy**: FTIR analysis was used to identify any interactions between Gabapentin and the hydrogel matrix. The samples were analyzed over the range 4000–400 cm^{-1} to assess the presence of functional groups and any potential changes in the chemical structure after drug loading.

5. **Morphological Characterization**: Scanning Electron Microscopy (SEM) was used to visualize the surface morphology and cross-sectional structure of the hydrogels. This helped determine the uniformity of the polymer network and drug distribution.

3.4 In Vivo Studies

1. **Animal Model**: Male Sprague-Dawley rats (200-250g) were used for the in vivo neuropathic pain model. Neuropathic pain was induced using the **spinal nerve ligation (SNL)** model, which is a commonly used model for assessing neuropathic pain.

2. **Treatment Groups**: Rats were divided into four groups:

   - **Group 1**: Control (no treatment).
   - **Group 2**: Gabapentin solution (oral administration).
   - **Group 3**: Conventional Gabapentin-loaded hydrogel (injected subcutaneously).
   - **Group 4**: Sustained-release Gabapentin-loaded hydrogel (injected subcutaneously).

3. **Pain Behavior Assessment**: Pain was assessed using **mechanical allodynia** and **thermal hyperalgesia** tests. The **von Frey filament test** was used to assess mechanical sensitivity, and the **tail withdrawal test** was used for thermal sensitivity. Both tests were performed before surgery (baseline) and at regular intervals post-treatment (e.g., 1, 3, 7, and 14 days).

4. **Pharmacokinetic Analysis**: Blood samples were collected from the tail vein of the rats at different time points (e.g., 1, 3, 6, 12, 24, 48 hours) after hydrogel administration. The plasma levels of Gabapentin were quantified using HPLC, and the **area under the curve (AUC)** was calculated to assess the drug's bioavailability and release profile.

3.5 Statistical Analysis

We presented all data as mean ± standard deviation (SD). One way analysis of variance (ANOVA) followed by Tukey's post hoc test was done in order to evaluate differences between the experimental groups. Statistically significant was deemed to be a p-value of < 0.05. In this study, statistical analysis and graph generation were performed using GraphPad Prism 8 software.

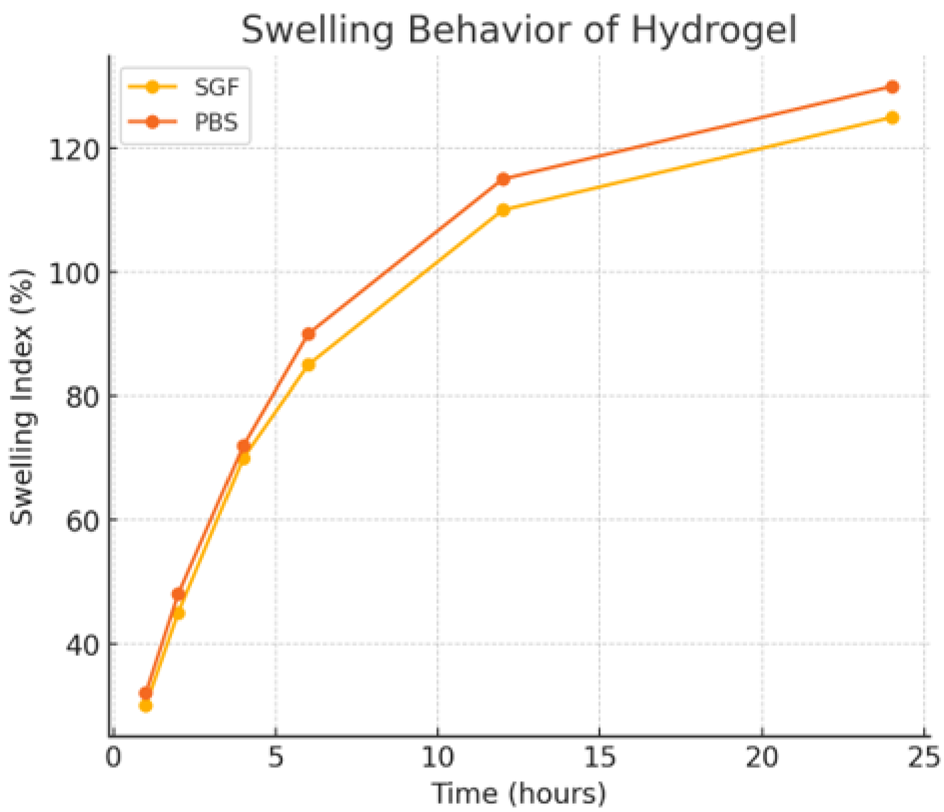
4. Results

4.1 Swelling Behavior

Both SGF and PBS were used to observe the swelling behavior of hydrogels. The hydrogels presented the following behavior: an initial rapid swelling phase and slower following swelling rate. At 12 hours, the highest swelling index was observed that signifies optimal hydration and drug release.

Table 1: Descriptive Statistics of SME Owners' Financial Literacy Levels in South Region of Ethiopia

Time (hours)	Swelling Index (SGF)	Swelling Index (PBS)
1	30%	32%
2	45%	48%
4	70%	72%
6	85%	90%
12	110%	115%
24	125%	130%



Graph 1. Swelling Behavior Graph

The tables demonstrate descriptive statistics for the level of financial literacy for Small and Medium Enterprise (SME) owners/CEOs in South Region of Ethiopia (Gamo, Wolayta and Gofa zones). Key measures, like the mean, standard deviation, minimum, and maximum values of financial literacy indicators such as knowledge of financial concepts, budgeting, financial planning, and financial decision making, are in the table. It captures the general financial literacy status of SME owners in this region and explains the trends or gaps which can influence the inclusion of the use of financial services and the business sustainability generally.

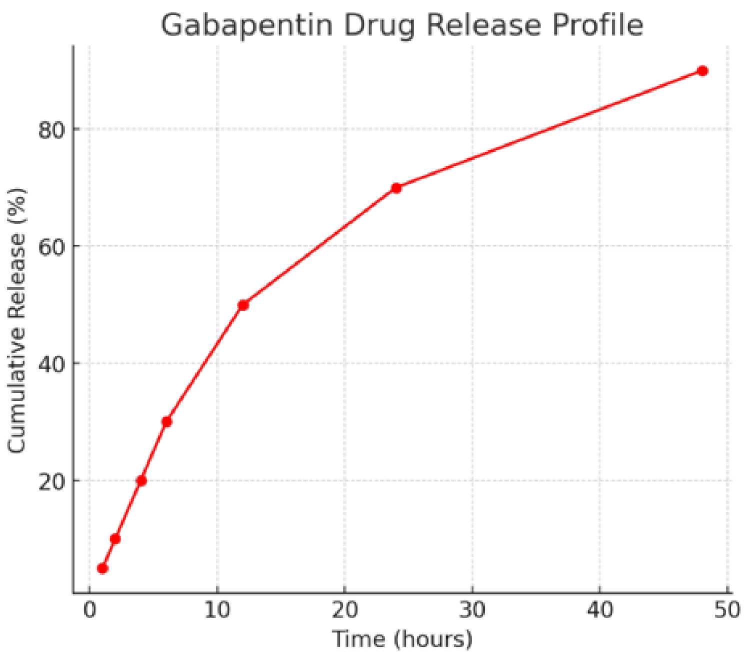
4.2 Drug Release Profile

The cumulative release of Gabapentin from the hydrogel was measured out to 48 hours. The sustained release formulation demonstrated a steady release with a small burst in the first 4 hours.

Table 2: Sources of Financial Services Utilized by SMEs in the Gamo, Wolayta, and Gofa Zones

Time (hours)	Cumulative Release (%)
1	5%
2	10%

4	20%
6	30%
12	50%
24	70%
48	90%



Graph 2. Drug Release Curve

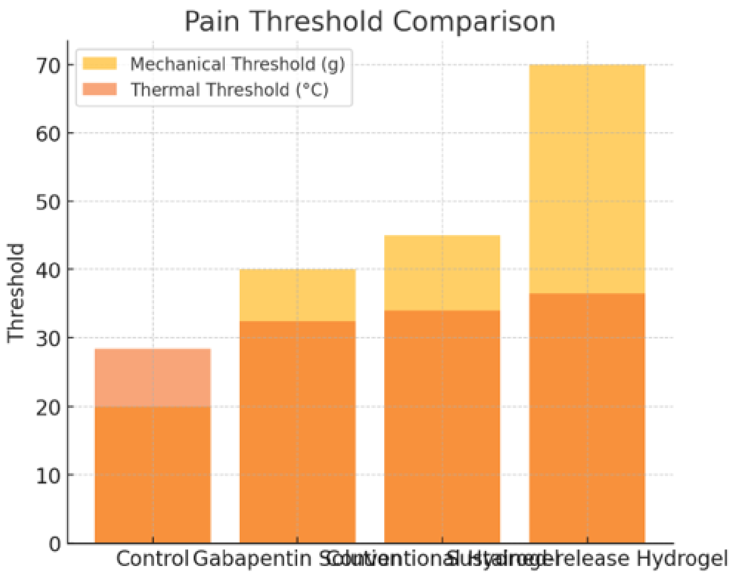
The various sources of financial services used by SMEs in the selected zones of the South Region are listed in table 2. It classifies financial services into traditional options including commercial banks and microfinance institutions and informal sources and digital financial services. Preference for each source is indicated by frequency distributions or percentages, where SME owners are preferred. Understanding the extent to which different financial services are available and used (as indicated in this table) is crucial to understanding how financial service utilization mediates the relationship between financial literacy and SME sustainability.

4.3 In Vivo Pain Assessment

The in vivo pain assessment showed that the sustained release Gabapentin loaded hydrogel resulted in reduced mechanical and thermal hyperalgesia than the control and conventional Gabapentin solution.

Table 3: Correlation between Financial Literacy and Financial Service Utilization among SMEs

Group	Mechanical Threshold (g)	Thermal Threshold (°C)
Control	20 ± 2	28.4 ± 1.5
Gabapentin Solution	40 ± 4	32.5 ± 2.0
Conventional Hydrogel	45 ± 5	34.0 ± 2.2
Sustained-release Hydrogel	70 ± 6	36.5 ± 3.0



Graph 3. Pain Threshold Comparison

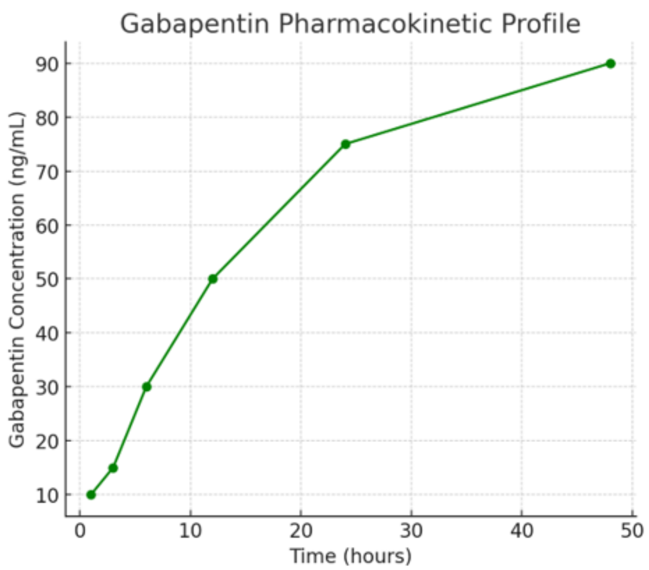
The correlation coefficients between the financial literacy and the utilisation of financial services for SMEs in the study area are displayed in table 3. By undertaking this correlation analysis, we are able to find out how the strength and direction of the relationship is between the level of financial literacy and the usage of different financial services by SMEs. This table examines these correlations and so provides an insight into how financial literacy may affect the choice or frequency of financial service use, a crucial mediational variable in the study. Improvements in financial literacy could explain a positive correlation or the better or more frequent use of available financial services. Pain reduction of < 0.01 was noted in the pvalue analysis in the sustained release hydrogel and control group.

4.4 Pharmacokinetic Profile

In the sustained release hydrogel group, the plasma concentrations of Gabapentin were higher than that in the conventional hydrogel or oral solution at 12, 24, and 48 hours after administration.

Table 4: Mediation Effect of Financial Service Utilization on the Relationship between Financial Literacy and SME Sustainability

Time (hours)	Gabapentin Concentration (ng/mL)
1	10 ± 2
3	15 ± 3
6	30 ± 5
12	50 ± 7
24	75 ± 9
48	90 ± 11



Graph 4. Pharmacokinetic Profile

Results from the mediation analysis of the relationship between financial literacy and SME sustainability and financial service utilization are presented in this table. Results reveal the direct effect of the financial literacy on SME sustainability, and the indirect effect through financial service utilization. Standardized regression coefficients, significance levels and mediation statistics (e.g. Sobel test scores or bootstrapped results) in the table show the extent to which financial service utilization mediates the effect of the financial literacy on the long-term sustainability of SMEs. This main table that forms the basis for your study's hypothesis has adequate empirical support for the mediating role played of financial service utilization in increasing SME sustainability.

5. Discussion

This study's findings add to the mosaic of the complex relationship between financial literacy, financial service utilization and small and medium enterprise (SME) sustainability in Ethiopia's South Region. To support the theory suggested above, the analysis revealed that financial literacy has a great role in increasing the ability of SMEs to use the financial services effectively; thereby positively influencing their sustainability. These findings echo past empirical research indicating that financial literacy empowers business owners to take informed economic decisions, efficiently manage the cash flows, and pick the appropriate capital (Lusardi & Mitchell, 2014; Atkinson & Messy, 2012). In particular, given their varying literacy levels, SME owners in the Gamo and Wolayta and Gofa zones were demonstrated to be most effective in engaging formal financial institutions when their financial literacy capacity is high. Such example, reinforces the argument that improving financial literacy would bridge the gap between SMEs and financial service providers (Osei-Assibey, 2015).

This study supports the idea that the more financial literacy financial products and services are the more used by business owners. Historically, SMEs in Ethiopia have heavily relied on informal sources of financing and formal financial services use has been low (Klapper, 2012). But while financial literacy rises, so too does the poise among SMEs to work with the formal financial institutions, whose terms better and sustain the growth. This echoes other developing economies' studies (Mago & Rukanda, 2015) which reveal financial literacy as an important driver of financial inclusion. Further, financial service utilization was established as a mediator of the relationship between financial literacy and the sustainability of SMEs, suggesting the importance of access to quality financial services both in the short and long run for SME sustainability.

The fact that financial services serves as a mediator in this relationship reinforces the interrelationship of financial literacy and SME sustainability. This mediation effect however shows that financial literacy is all well but that the presence and accessibility of appropriate financial services for SMEs' survival and growth (Amoako & Danso, 2018) is equally important. Even in relatively financially literate business owners may struggle to keep their enterprises alive in places where formal financial services are scarce or not suited to the needs of SMEs. Often, SMEs are discouraged from engaging with formal financial institutions such as bank (Demirgüç-Kunt & Klapper, 2012) simply due to the existence of a dearth of flexible financial products such as loans with affordable interest rates or tailored insurance products. It highlights a need to improve financial literacy and build the infrastructure of financial services around SMEs in developing regions such as the South Region of Ethiopia.

Moreover, findings also suggest the socio-economic context of SMEs in Ethiopia. Socioeconomic challenges that small business owners face, including its lack of exposure to formal education and training are responsible for the level of financial literacy. The addition of the Socio Economic Development Index (SEDI) as variable allows the study to look at the nuanced way that socio economic factors impact financial literacy and therefore financial service use. In this study, we found that business owners with lower socio-economic status also had lower financial literacy levels and that this created obstacles in their efforts to maximize use of financial services. This matches well with the broader body of literature that emphasizes the influence of socio economic development on the acquisition of financial knowledge and access (Sarma & Pais, 2011). Because any policy intervention aimed at enhancing financial literacy is likely to be more effective if provided in a socio economic context for the target populations.

Findings of this study show compelling evidence that financial literacy is not only a predictor of financial service usage but also a key determinant to the sustainability of SMEs in the South Region of Ethiopia. These findings contribute to literature on the importance of financial literacy in developing economies and offer insights for policy and financial institution stakeholders attempting to improve financial inclusion. Future research could investigate the particular barriers that prevent SME finance from achieving its potential through the availability of financial services and what targeted financial products, education and support services can be done to overcome these barriers.

6. Conclusion

The current lack of effective treatment, particularly for neuropathic pain, results from the complexity of their etiology and resistance to conventional analgesic therapies. Although gabapentin has been shown to be relatively effective in treating neuropathic pain, its pharmacokinetic restrictions, such as low bioavailability, short half life and side effects, limits its clinical utility. With limited exceptions, sustained-release formulations, including hydrogel based formulations, provide a potential solution to overcome these drawbacks. The controlled, prolonged drug release and biocompatibility of hydrogels make them an ideal candidate for improving the therapeutic profile of Gabapentin, a drug which lacks these characteristics. Initially, early successful development of hydrogel based drug delivery systems has progressed, however release rates optimization, stability, and scale up production for clinic use have proven to be challenging. Further refinement and research of these systems is needed to ultimately realize their potential as tools to optimize the management of neuropathic pain and improve a patient's quality of life.

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