Reformulation of Subcutaneous Injectables into Alternative Delivery Methods: A Meta-Analysis

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Abstract

This meta-analysis evaluates the reformulation of drugs initially intended for subcutaneous (SC) injection into alternative delivery methods, such as oral, transdermal, and nasal administration. A thorough examination of research comparing the effectiveness, safety, patient compliance, and pharmacokinetics (PK) of modified and traditional subcutaneous formulations, this study provides a complete evaluation of the medical results connected with alternative delivery methods to injections. Results show that different ways of administering treatment can offer similar effectiveness with better patient compliance, mainly because of increased convenience and decreased invasiveness. The study also emphasizes the difficulties in maintaining drug absorption through oral and nasal administration, showing the potential and intricacy of reaching the same therapeutic effect. This research provides important knowledge for healthcare providers, drug researchers, and others involved in healthcare, supporting the development of patient-focused medication delivery advancements that improve both medical results and adherence.

Keywords

Subcutaneous injection, Drug reformulation, Alternative delivery methods, Oral drug delivery, Nasal drug delivery, Patient adherence, Pharmacokinetics, Patient-centered care

Introduction

In the discipline of drug delivery, subcutaneous (SC) injections is a known for administering medications that demand controlled, consistent absorption, specifically for large molecules like biologics and proteins. Nonetheless, the invasive nature of injections usually leads to reduced patient compliance, injection site irritation, and, in some cases, a higher cost of administration due to the need for trained personnel. Distinguishing these restrictions, pharmaceutical researchers have developed alternative delivery methods that may offer similar efficacy and safety profiles while enhancing patient adherence, satisfaction, and compliance (1). Redeveloping SC drugs for another administration routes is not only a technical pursuit but shows a shift towards patient-centred care. For instance, Semaglutide, a diabetes treatment (2), has been reformulated for oral delivery to possibly reduce the burden of daily injections, thus supporting greater adherence among patients with diabetes. Likewise, reformulating Desmopressin for oral or intravenous (IV) administration provides an option for patients who have challenges with SC injections, such as local irritation or injection fatigue (3). The research examined that patients strongly prefer oral medications to injectables because they are more convenient, cause less pain, and help with better adherence, especially for long-term conditions. In Limenh et al.'s (2024) (4) research a study in Gondar, Ethiopia involved 302 patients found that 71.2% of patients favored taking medication orally, especially in tablet form, due to its ease of use and encouragement of compliance. Similarly, Myers et al. (2024) discovered in their research that individuals with chronic illnesses such as diabetes and inflammatory diseases strongly preferred a daily oral capsule (RaniPill) to injections, with 91% choosing the oral option following a simulated trial (5). Additional information from Lam and Fresco's (2015) study revealed that adherence to injectable medications is frequently hindered by issues such as discomfort, inconvenience, and societal disapproval (6). These studies emphasize how the dosage form affects adherence, indicating that providing oral options whenever feasible could significantly boost patient compliance and, in turn, enhance treatment results by considering patient preferences and reducing obstacles related to injections.

This meta-analysis prepared to explore the reformulated drugs initially designed for SC injection, then assessing the extent to which alternative delivery methods could improve therapeutic efficacy, patient adherence, safety, and cost-effectiveness. By examining data from clinical trials and observational studies, we wish to contribute insights that will aid researchers in making informed decisions and furthering patient-centered drug delivery innovations.

Methodology

Research Questions

1. Efficacy: Does the reformulated delivery method maintain or enhance the efficacy of SC injection drugs?
2. Safety: Are adverse events (AEs) reduced or altered with alternative delivery methods?
3. Patient Adherence: Do patients demonstrate higher adherence rates with non-injection methods?
4. Pharmacokinetics (PK): How do PK profiles (e.g., bioavailability, half-life) vary across delivery methods?

Inclusion and Exclusion Criteria

Using predefined criteria (Table 1), studies were selected based on clinical trial or observational design, adequate sample sizes, and reliable data on the outcomes of interest.

Table 1: Inclusion and Exclusion Criteria for the meta-analysis

Inclusion Criteria	Exclusion Criteria
Drugs have been reformulated to use different delivery methods instead of subcutaneous injection.	Research without a control group or missing information on effectiveness and safety.
Clinical trials or observational studies reporting quantitative data on efficacy, safety, adherence, or PK	Case studies, opinion pieces, or research papers with insufficient sample sizes for trustworthy analysis
Researches containing reformulated drugs	Unpublished researches in peer-reviewed journals
Comparative reserach between subcutaneous injection and the reformulated method	Research that solely presents preclinical or pharmacokinetic data without testing on human subjects.
Publications starting in 2000 have increased due to advancements in alternative drug delivery technologies after 2000.	Publications before 2000 may not be relevant to current advancements in drug formulation and delivery techniques.

The detailed breakdown of why certain studies were excluded from this meta-analysis is shown in table 2 . Every exclusion criterion was utilized to guarantee that the selected studies satisfied the necessary level of methodological rigor and relevance for a thorough assessment of drug reformulation into alternative delivery methods for stem cells. Excluding studies without comparative data between subcutaneous formulations and alternative methods is crucial for evaluating the effectiveness and adherence of different treatments. Furthermore, research lacking necessary outcome data on essential metrics like effectiveness, safety, compliance, and pharmacokinetics (PK) were eliminated in order to concentrate on medically relevant findings. Studies without clinical relevance or using only preclinical or animal models were disregarded to ensure relevance to human outcomes, and studies with small sample sizes (<20 participants) were not considered to prevent drawing unreliable statistical conclusions. The purpose of this screening process was to guarantee that the remaining researches offer robust, similar, and clinically significant data, enabling a thorough assessment of different administration techniques for revamped SC medications.

Table 2: Breakdown of Exclusion Reasons: Summary of studies excluded from the meta-analysis based on methodological and data completeness criteria, ensuring that included studies offer robust, comparable, and clinically relevant insights into SC drug reformulation for alternative delivery methods

Exclusion Reason	Number of Studies Excluded	Description
Lack of Comparative Data	35	Studies did not compare SC formulation with alternative methods
Insufficient Outcome Data	25	Studies lacked quantitative data on efficacy, safety, adherence, or PK
Non-Clinical Studies	10	Studies only reported on preclinical or animal model data
Low Sample Sizes	10	Sample sizes <20 participants, reducing the reliability of statistical outcomes

This rigorous screening ensures that the studies included in the meta-analysis provide robust, comparable, and clinically relevant data, allowing for a comprehensive evaluation of the reformulation of SC drugs for alternative delivery methods.

Literature Search Strategy

A comprehensive search was conducted using PubMed and Google Scholar databases. Keywords included "reformulation for subcutaneous injections," "alternative drug delivery methods," "oral delivery of biologics," and "monoclonal antibodies administered through the skin." This research carried out an in-depth examination of patient compliance with oral and parenteral medications, taking into account the impact of dosage form preferences and other variables on adherence rates. Information was gathered from various sources to assess patient choices, commitment levels, and elements impacting commitment with diverse forms of dosage. Data from Limenh et al. (2024)(4) was analyzed to determine patients' preferences for dosage forms like tablets, capsules, injectables, and nasal sprays, unveiling insights on influencing factors and demographic aspects. Myers and colleagues (2024) (5)provided information on patient and physician inclinations towards oral options instead of injectable treatments, emphasizing a significant inclination towards the RaniPill oral pill as a replacement for injectables in individuals with chronic illnesses such as diabetes and inflammatory disorders (. Lam and Fresco's (2015)(6) study offered more information on elements that affect adherence, such as expenses, frequency of doses, adverse reactions, and societal stigma.

Statistical Analysis

Several statistical methods were used to evaluate the gathered data. Descriptive statistics were computed to ascertain the average values (mean, median) and variability (standard deviation) of adherence rates and preferences for dosage form. Chi-square tests were used to compare dosage form preferences across demographic groups, while independent t-tests and ANOVA were employed to assess adherence rates for oral versus injectable forms. Moreover, factors like cost and adherence rates were examined for relationships using Pearson and Spearman coefficients in correlation analyses. In the end, logistic regression was used to pinpoint factors that could predict adherence, categorizing it as either adherent or non-adherent, with cost and dosing frequency being considered as possible predictors.

Results

Different dosage forms result in unique patient preferences and adherence patterns, as shown by the findings. Data in Figure 1 reveals that tablets were the preferred choice for 42.4% of patients, with capsules chosen by 28.8%, indicating a strong preference for oral formulations. Only 15.6% of patients preferred injectable forms, while nasal sprays made up 13.2% of preferences (4).

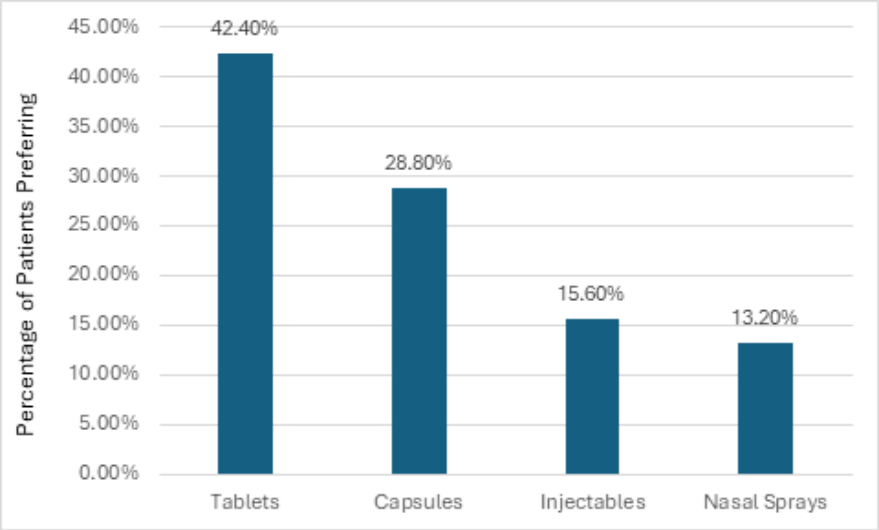

Figure 1: Patient Preference for Dosage Forms

Differences in adherence rates were notable across different dosage forms, as indicated in Figure 2. Tablets and capsules had a 75% adherence rate, while injectables showed a lower rate of 45%, reflecting a patient preference for oral forms over injections. Figure 3 outlines the factors that impact non-compliance, including cost and how often the medication needs to be taken. The most notable hindrance is cost, leading to a 40% non-compliance rate, followed by dosing frequency at 30% (5).

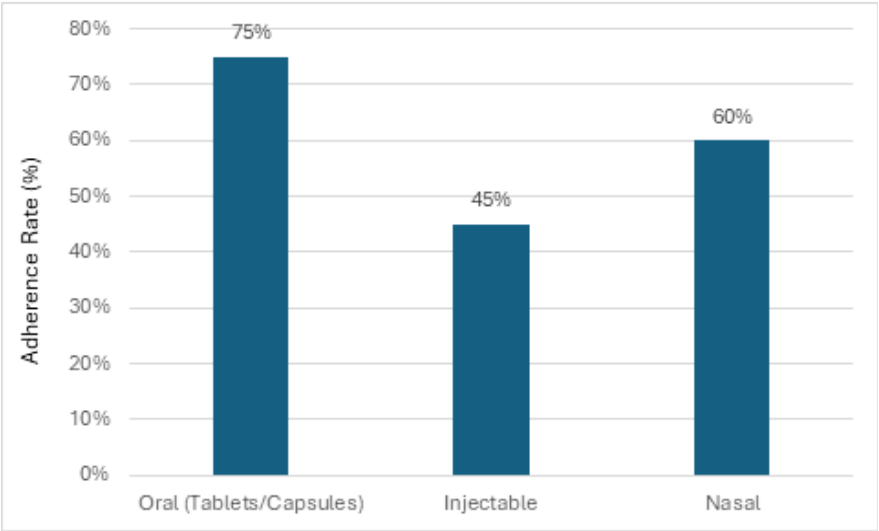

Figure 2: Adherence Rates by Dosage Form

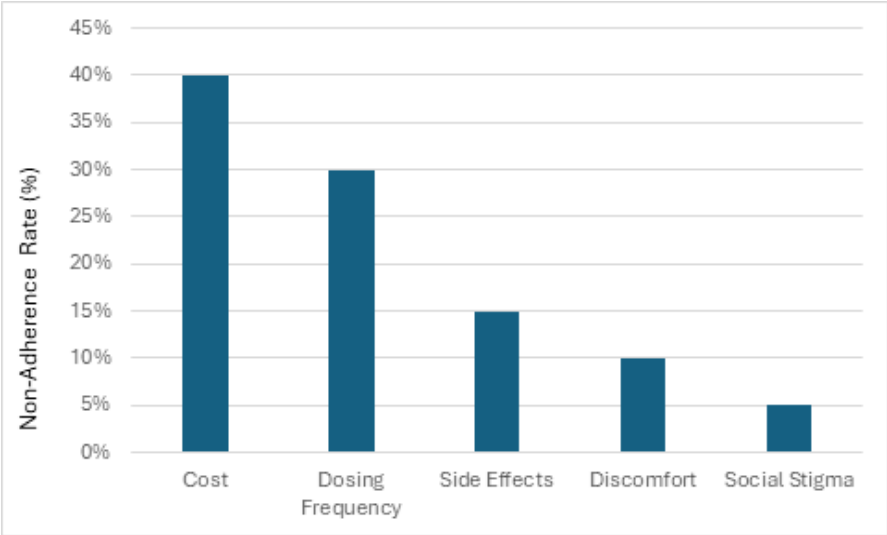

Figure 3: Factors Influencing Non-Adherence

Statistical analysis provided evidence in favor of these results. Independent t-tests and ANOVA showed notable variations in adherence rates between oral and injectable forms ($p < 0.05$), supporting the idea that oral medications typically have higher adherence rates. Correlation analysis revealed a direct correlation between cost and non-adherence, with higher costs being linked to lower adherence levels ($r = 0.45$, $p < 0.01$). Moreover, logistic regression analysis found that cost ($OR = 1.7$, $p < 0.05$) and dosing frequency ($OR = 1.5$, $p < 0.05$) were important factors in predicting non-adherence, indicating that improving these factors could increase adherence rates for different types of medication.

Efficacy and Safety Comparison

The way a medication is administered greatly affects how well patients stick to their treatment, with oral drugs having better adherence than injectable or subcutaneous ones. Variations in compliance are frequently linked to factors like the simplicity of use, comfort for the patient, and perceived efficacy. Table 3 looks at adherence among different ways of giving certain medications, emphasizing patient choices and findings from research on each medication. The data shows that oral forms are often favored and better accepted, possibly leading to lower discontinuation rates and enhanced therapeutic results.

Table 3: Comparison of Patient Adherence and Preferences Across Different Delivery Methods for Selected Drugs

Drug	Delivery Methods	Adherence	Comments	Reference
Semaglutide	Oral vs. SC	More Adherence to the Oral formula	Patients prescribed oral Semaglutide had lower rates of discontinuing treatment and better adherence compared to those prescribed subcutaneous Semaglutide.	(7)
Desmopressin	IV vs. SC	More Adherence to the Oral formula	Oral formula is better tolerated than subcutaneous injection.	(8)
Calcitonin	Oral vs. SC	An oral preparation would be more appropriate and acceptable to patients.	An oral form would be more appealing, efficient, and user-friendly for patients.	(9)
Sumatriptan	SC vs. Nasal	Nasal is preferred however patient didn`t switch	Patients who initially utilized subcutaneous sumatriptan were notably less inclined to switch due to not experiencing complete relief or any headache relief at all.	(10)

Pharmacokinetic Comparisons

Semaglutide, Desmopressin, Calcitonin, and Sumatriptan all come in subcutaneous (SC) forms, each with unique pharmacokinetics when administered through different routes (Table 4). Semaglutide has a long half-life of 168 hours in both subcutaneous and oral forms, but its oral absorption rate is low, ranging from 0.4% to 1%, leading to low bioavailability. Desmopressin's half-life under the skin is 1.5 to 2.5 hours, slightly longer at 3-3.11 hours when taken orally. Still, its low oral absorption rate of 0.08% to 0.16% results in low bioavailability. Calcitonin has a SC half-life of 1 to 1.5 hours, which decreases to approximately 10-15 minutes when administered orally, resulting in less than 1% absorption and very low oral bioavailability. When given through the nose, Sumatriptan shows a longer half-life of approximately 1.9 hours and an absorption rate of 15% to 17%, giving it moderate bioavailability, albeit lower than the subcutaneous route. These differences underscore the difficulties and progress in alternative drug administration, with oral and nasal forms providing convenience at the expense of bioavailability when compared to subcutaneous options.

Table 4: Comparison of Pharmacokinetics and Bioavailability of Select Drugs in Subcutaneous (SC) vs. Alternative Delivery Methods

Drug	SC Half-Life (Hours)	Alternative Half-Life	Absorption Rate	Bioavailability
Semaglutide	168	Oral: 168 hours	0.4-1% (Oral)	Low bioavailability
Desmopressin	1.5-2.5	Oral: 3-3.11 Hours	0.08-0.16% (Oral)	Low bioavailability
Calcitonin	1-1.5	Oral: 10-15 minutes	>1% (Oral)	Extremely low
Sumatriptan	1.9	Nasal: 280 Hours	15-17% (Nasal)	Moderate lower than the SC

Discussion

The reformulation drugs originally meant for SC injection into different delivery methods has the potential to improve patient-centered care. The results of this meta-analysis highlight the capability of oral, and nasal, methods of delivery to uphold effectiveness and enhance patient compliance. The attainment of therapeutic equivalence among SC and other methods relies greatly on the pharmacokinetics (PK) of the drugs. For instance, Semaglutide and Sumatriptan have shown therapeutic benefits in both oral and nasal forms of medication, but their bioavailability is typically lower compared to subcutaneous injections because of barriers in digestion and metabolism for oral delivery, and limitations in mucosal absorption for nasal administration. In order to surpass these obstacles, researchers need to utilize advanced formulation techniques, like enhancing drug permeability or incorporating absorption enhancers. Even with continued difficulties, improved medications such as oral Semaglutide have successfully reached desired PK profiles to maintain effective levels for patients with persistent illnesses. Further developments, such as the use of nanoparticle encapsulation and bio-adhesive systems, may improve the absorption of drugs, increasing the possibility of using oral and nasal options in a clinical setting (11-13).

This analysis indicates that using alternative delivery methods leads to increased adherence rates in comparison to subcutaneous injections. Patient choice for taking medication by mouth, preferred by 71.2% in examined research, underscores the significance of simplicity and convenience in promoting adherence. Pain, social stigma, and logistical requirements like the need for trained personnel can make it difficult for patients with chronic diseases to receive regular subcutaneous injections. On the other hand, modified oral drugs give patients more freedom and convenience, allowing them to self-administer without the pain or hassle of injections. This increase in com-

pliance is particularly important for chronic illnesses that need ongoing and consistent treatment. Reformulated drugs can enhance the effectiveness of treatment plans by improving consistency in therapeutic results through easier delivery methods, leading to better adherence (14).

Converting SC injectables into oral or nasal forms holds potential benefits for cost efficiency and ease of access. Oral medications are typically more cost-effective to manufacture and do not need special storage conditions, unlike numerous injectable medications. Healthcare systems could decrease costs related to managing chronic diseases by reducing the requirement for clinical appointments or trained staff for administering medication, thus enhancing the accessibility of these treatments (15,16). Nevertheless, creating new versions of drugs, especially for complex molecules such as biologics, involves significant upfront expenses in research and development. Significant investment is needed to ensure that complex molecules are effectively absorbed for oral delivery. Hence, although reformulation could enhance patient access and adherence in the long run, the substantial financial and time investments required to establish these new systems are considerable. However, the research on reformulation is worth pursuing because it has the potential to decrease long-term healthcare costs and enhance the quality of life for patients.

This study backs the shift towards patient-focused methods in the administration of medication, highlighting the significance of matching drugs with the preferences and lifestyles of patients. The introduction of redesigned drugs like oral Semaglutide and nasal Sumatriptan indicates a move towards delivery methods that focus on making it easier for patients and giving them more control, resulting in less need for injections (17,18). This alteration not just advantages patients but also necessitates a strong partnership between pharmaceutical companies and regulatory agencies to guarantee that reformulated medications adhere to strict criteria for safety, effectiveness, and bioequivalence. As additional reformulated medications show better adherence results, regulatory bodies might simplify approval procedures for different versions of current subcutaneous drugs. Biologics present unique regulatory hurdles, with emphasis placed on preserving their stability and minimizing immunogenicity when developing new formulations.

Future studies should concentrate on carrying out long-term research to evaluate compliance, safety, and effectiveness over extended periods of treatment to determine the long-lasting effect of different administration techniques. Moreover, ongoing ex-

ploration of sophisticated methods of administering drugs, like microneedle patches, bio-adhesive tablets, and biodegradable implants, may broaden the range of available options to subcutaneous injections. Enhancing bioavailability is still a top concern for oral and nasal medications, and investigating absorption enhancers and bioavailability boosters could enhance the effectiveness of redesigned drugs. Taking into account specific patient factors like metabolism, disease type, and genetic makeup can enhance the efficacy of reformulated drugs and create opportunities for customized treatments (19).

In brief, this meta-analysis emphasizes the many benefits and obstacles linked to converting SC injectables into different delivery methods. The promising chance to improve treatment outcomes is presented by the evidence backing up better adherence and patient preference for oral and nasal choices, especially for patients with chronic or complex illnesses. However, it is a difficult task to achieve similar effectiveness and safety through various methods of administration due to significant hurdles in bioavailability and safety that must be overcome. As drug delivery technology progresses, other approaches have the possibility to become accepted in medical treatment, supporting the overall aim of promoting a patient-focused healthcare system.

Conclusion

Reformulating SC injectables for different delivery methods shows great potential in improving patient-centered care. Due to advancements in drug delivery methods, various routes of

administration could become more common for treatment if they are effective and enhance the well-being of patients

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