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Original Article

Development and evaluation of transdermal gel for pain relief

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ABSTRACT

The study was to develop transdermal gel formulations for the delivery of aspirin and paracetamol. Compared to more conventional approaches like oral, injectable, and inhaler administration, transdermal medication delivery through the skin has a number of benefits. These benefits include self-administering simplicity, non-intrusiveness, usability, cost, and the capacity to maintain sustained plasma drug concentrations over prolonged periods of time. Two polymers in creating transdermal gels Carbopol-934 and Sodium Alginate were assessed. Carbopol-934 was chosen because of its capacity to improve drug retention and limit drainage, allowing for the drug's sustained release. The gel compositions were thickened and stabilized using sodium alginate. Pre-formulation tests, rheological characteristics, spread-ability, pH levels, homogeneity, and potential for skin irritation were assessed for both Carbopol-934 and Sodium Alginate gel formulations. In order to avoid application-related skin irritation, the pH levels of the gel formulations were closely checked to make sure they stayed within the permitted range. In comparison to other Carbopol-934 and Sodium Alginate formulations tested, Carbopol-934 gel formulation F3 showed the best spread-ability (S=95.9). Due to its constant qualities, including acceptable spread-ability, pH range, and homogeneity, without producing any skin irritation, this formulation was deemed satisfactory. In conclusion, the creation of a transdermal gel formulation using Carbopol-934 as the main polymer matrix shows potential for delivering these medications through the skin. This study highlights the potential of transdermal drug delivery devices as a practical and efficient replacement for conventional methods of administering painkillers.

Keywords: *Transdermal Drug Delivery System; Stratum corneum; Topical Gel; Carbopol-934; Sodium alginate; Paracetamol; Aspirin.*

Introduction

Transdermal drug delivery systems are intended to continuously spread a therapeutically effective amount of medication across the skin of a patient. Approximately 40% of the medication candidate products currently undergoing clinical testing are connected to the transdermal system [1]. The first pass metabolism, gastrointestinal metabolic degradation, and discomfort linked to oral administration are avoided by topical drug delivery systems. This method of drug delivery is ideal for treating skin-related disorders locally [2]. Transdermal administration is required for drugs like non-steroidal anti-inflammatory drugs (NSAIDs), which could have adverse systemic effects [3]. Direct gastrointestinal discomfort is supposed to be lessened by using topical formulations rather than oral ones, although effectiveness is a big concern [4].

Paracetamol is currently marketed as an analgesic and antipyretic. More focus needs to be given to properly

evaluating the dangers of long-term use at therapeutic levels because chronic paracetamol use has less analgesic effect than previously thought. This makes it possible for authorities to recommend that it be made available in OTC medications and helps clinicians balance potential risks against likely benefits for particular patients. It is well known that consuming too much paracetamol might have negative consequences right away [05]. In clinical settings, paracetamol typically relieves pain from mild to moderate inflammation, such as that from sprains and contusions, but not from people who have severe inflammation from conditions like rheumatoid arthritis or acute gout. The indirect inhibition of the COX enzymes by inhibition of its POX binding site, hence lowering the activity at the COX site, is the hypothesized reason for this result [6]. This is in contrast to how NSAIDs and coxib's directly block the COX binding sites [6].

Acetylsalicylic acid (aspirin) has been used in medicine for its analgesic, antipyretic, and anti-inflammatory qualities ever since Hippocrates. Similar to other non-steroidal anti-inflammatory medicines, the analgesic effect was achieved by inhibiting prostaglandin synthesis at several steps, which led to the inhibition of cyclooxygenase enzymes (COX) in the end. Aspirin irreversibly inhibits both COX-1 and COX-2, the constitutive and inducible forms of COX, respectively. COX-2 produces therapeutic effects, whereas COX-1 inhibition causes irritation of the gastric mucosa and impairs kidney function. These enzymes increase the production of prostaglandin E2. An alternative administration route that avoids the gastrointestinal tract is offered by transdermal delivery systems. It is less intrusive, safer, and more agreeable to patients, especially when aspirin is used for extended periods of time. In addition to avoiding direct contact with COX-1, which is found in the gastric mucosa, cutaneous aspirin also has a low absorption [7]. By using Carbopol-934 and sodium alginate in the gel matrix, NGs' skin penetration characteristics can be successfully altered, changing them from transdermal to topical drug delivery systems. The inclusion of NEs (Nanoemulsions) in hydrogel exemplifies excellent potential for several therapeutic applications (such as topical or all-encompassing management) [8,9].

Experimental

Material

Paracetamol was kindly provided by SD fine chemical LTD. Tarapur (Maharashtra), Aspirin is obtained from Nice chemical LTD. Kochi (Kerala) and other material used were Carbopol-934 [Loba chemical LTD. Maharashtra], Sodium alginate [Nice chemical LTD. Kochi (Kerala)], PEG-400 [SD fine chem limited. Mumbai (Maharashtra)] and Ethanol [Changshu Hongsheng Fine chemical Co. Ltd. Changshu city, Jiangsu Province]. All organic solvents used were of high-performance liquid chromatography (HPLC) grade.

Preparation of Paracetamol-Aspirin gel

Preparation

Pain relief gel was prepared by dissolving carbopol-934 and Sodium alginate in 60 ml of distilled water to give a final concentration with continuous mixing using a magnetic stirrer until a homogenous gel was formed. The gel was set aside for few minutes until the bubbles disappeared. Paracetamol (1g) and Aspirin (0.5g) was mixed with ethanol to a level and incorporated into the gel. PEG-400 (10 ml) was also added, and 1 ml of Rose water was added with continuous stirring. Six different formulations (F_1-F_6) were prepared (In addition to the blank and reference product) by incorporating different permeation enhancers to the final gel, as shown in table. The gels were kept in plastic well-closed containers and stored at room temperature until the time analysis.

Table 1: Composition of the Pain relief gel formulation.

Chemical	F_1	F_2	F_3	F_4	F_5	F_6
Paracetamol	1 g	1 g	1 g	1 g	1 g	1 g
Aspirin	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
Carbopol-934	1.5 g	2.0 g	2.5g	_-	-	-
Sodium alginate	-	-	-	1.5 g	2.0 g	2.5g
PEG-400	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Ethanol	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Distilled water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Perfume	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

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Evaluation parameters of Transdermal gel of Aspirin and Paracetamol [10, 11]

Preformulation Studies

In order to create stable, safe, and effective dosage forms, the formulation scientist characterizes the physical, chemical, and mechanical properties of new pharmacological compounds during the preformulation stage of the research and development process. Preformulation should ideally start early in the discovery process so that the necessary physical and chemical information is available to aid in the identification of new chemical entities that join the development process. Possible interactions with other inert substances intended for use in the final dosage form were also taken into account in the current investigation throughout this evaluation. The data below must be taken into account.

pH measurement

Using a digital pH meter, the pH of several gel compositions was measured.100 ml of freshly prepared distilled water were added to 1 g of gel, which was then stored for two hours. Each formulation's pH was measured three times, with the average readings being computed.

Rheological study

The sample was put into the Brookfield Digital Viscometer's detachable sample holder, which was then inserted into a flow jacket mounted to the viscometer. The viscosity of the preparations was measured using a tiny sample adapter (RV-7 spindle) rotating at a speed of 20 rpm. The thermostat water jacket was used to circulate water to maintain the sample's temperature at 30 °C. Five minutes were given for the sample to settle before the reading was taken. In order to show potential gel flow behaviour, gel viscosity measurements were assessed using a Brookfield digital viscometer by applying increasing values of the shear rate. The sample was put into the Brookfield Digital Viscometer's detachable sample holder, which was then inserted into a flow jacket mounted to the viscometer. The viscosity of the preparations was measured using a tiny sample adapter (RV-7 spindle) rotating at a speed of 20 rpm. The thermostat water jacket was used to circulate water to maintain the sample's temperature at 30 °C. Five minutes were given for the sample to settle before the reading was taken. In order to show potential gel flow behavior, gel viscosity measurements were assessed using a Brookfield digital viscometer by applying increasing values of the shear rate.

Spreadability

The capacity to spread well is one requirement for a gel to attain the ideal quantities. It is a term used to describe the size of the area to which gel spreads easily when applied. The spreading value of a formulation affects how well it treats a condition. Glass slide and wooden block measuring tools were used to make the decision. Weights of approximately 2 g were added to the pan, and the amount of time it took for the upper slide (movable) to entirely separate from the fixed slides was recorded.

Spreadability was then calculated by using the Formula:

$$S = M.L/T$$

Where,

S = Spreadability
M= Weight tide to the upper slide
L = Length of a glass slide
T = Time taken to separate the slide completely from each other.

Homogeneity

The homogeneity of each formed gel was checked visually after it had been placed in the container. They underwent inspections to look them over and look for aggregates.

Stability study

Stability of the active ingredient must be a primary consideration when designing and evaluating dosage forms for medications in order to decide whether they should be accepted or rejected. The capacity of a certain formulation, in a specific container, to maintain its physical, chemical, therapeutic, and toxicological specifications is known as drug stability. The stability test requirements for drug registration applications in the European union, Japan, and the USA are described in the international conference on Harmonization (ICH) guidelines titled "stability testing of New Drug substance and product".

Stability studies as per ICH guidelines:

Long-Term Testing: 25 °C + 2 °C / 60 % RH + 5 % for 12 months.

Accelerated Testing: 40 °C + 2 °C / 75 % RH + 5 % for 6 months

Stability tests for the selected formulation were carried out for a month at 40 °C + 2 °C/75 °C + 5% RH. The chosen formulation was put into an aluminum or plastic container that was airtight. They were then tested for their physical appearance and drug diffusion at defined intervals in accordance with ICH criteria after being stored at 40 °C and 75% RH for one month.

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Skin irritation

Each formulation was evenly placed over a surface area of 2 cm2 in a quantity of 0.5 g. At 24 hours after applying different formulations, the skin was checked for any obvious changes, such as erythema (redness) and irritation.

pH measurement

The pH of various gel formulations was determined by using digital pH meter. 1 g of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

Results

Table 4: pH data of all formulations.

Formulation number	pH	pH	pH	Average
F_1	5.0	5.3	5.7	5.33
F_2	5.21	5.27	5.24	5.24
F_3	5.2	5.7	5.4	5.43
F_4	7.36	7.5	7.36	7.40
F_5	6.37	6.45	6.5	6.44
F_6	7.6	7.62	7.65	7.623

Spreadability

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application. The therapeutic efficacy of a formulation also depends upon its spreading value It was determined by wooden block and glass slide apparatus. Weights of about 2 g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides.

Table 5: Spreadability data of all formulations.

Formulation number	Sample 1 (In sec.)	Sample 2 (In sec.)	Sample 3 (In sec.)	Average	Spreadability
F_1	0.6	0.6	1.0	0.73	958
F_2	3.62	3.7	3.6	3.64	192.3
F_3	7.0	6.0	9.0	7.3	95.9
F_4	0.25	0.6	0.42	0.423	1654.85
F_5	1.2	1.6	1.35	1.383	506.15
F_6	2-1	2.3	1.62	2.0	350

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. The homogeneity result is similar to Patel Hiren et al. All formulation transdermal gels showed good homogeneity with absence of lumps.

Gel irritancy

Paracetamol and Aspirin Carbopol-934 gel formulations were white in color, homogeneous in texture and fell within a pH range of 5.0 to 5.5 which is compatible with normal skin pH in healthy people.

Paracetamol and Aspirin- Sodium alginate was pale yellow in color, homogeneous in texture and fell

within a pH range of 6.4 to 7.6. When the formulation was put on the skin for irritancy test, it showed no symptoms of rashes, redness, irritation or swelling throughout the test.

Discussion

Compared to oral administration methods, topical and transdermal medication delivery systems provide a number of benefits. However, it was discovered that the oral administration system of the drug had a significant number of negative effects. Paracetamol-Aspirin and here to discuss its oral dosage form's negative effects. To reduce the risk of skin irritation after application, the pH values of the carbopol-934 gel formulation (F1 to F3) and sodium alginate gel formulation (F4 to F6) ranged from 5.3±0.13 to 7.0±0.62. When compared to other carbopol-934 and sodium alginate formulations, in which carbopol-934 and PEG-400 were utilized as surfactants, formulation F3 (S=95.9) was shown to have good spreadability of carbopol-934 gel. The homogeneity of each manufactured gel was checked visually after it had been placed in the container.

Conclusion

Drug delivery through the skin has been both an intriguing and difficult study topic, represents the largest and most easily accessible organ of the body and its use for topical and systemic delivery of drugs has been well documented. Transdermal medication administration has a number of benefits over other traditional drug delivery methods such oral, injectable, and inhaler. Transdermal systems can be self-administered and are non-invasive, practical, and affordable. For extended periods of time, they can give a sustained plasma concentration profile. There are many transdermal formulations like lotions, creams, ointments, patches, etc. out of this gel is preferred. Transdermal gels are becoming more popular due to ease of application and better percutaneous absorption. The term gel is semi-solid, three dimensional, polymeric matrices comprising small amounts of solid dispersed in relatively large amount of liquid yet possessing more solid like character. These systems form a three-dimensional, polymeric matrix in which a high degree of physical reticulation has been compromised. Gel formulations provide better application property and stability in comparison to cream and ointments. Paracetamol and Aspirin are the drug of choice in treatment of pain relief. Paracetamol is thought to reduce the intensity of pain signals to the brain and reduce fever, Aspirin prevents your body from producing prostaglandins, which decreases discomfort, swelling, and high body temperature. Transdermal gel of paracetamol-aspirin gel was prepared with aim to deliver the drug through transdermal route as it provides quick action in comparison of oral route. In preliminary study, Carbopol-934 and Sodium Alginate (Polymers) were evaluated for their efficiency to form a transdermal gel, carbopo-934 used because they are increased the drug retention time, prevented drug drainage, and thus released the drug for prolonged periods and sodium alginate used for thickening and stabilize the mixtures. Different parameters were studied like pre-formulation studies, rheological studies, spreadability, pH, homogeneity and skin irritation, were carried out for transdermal gel formulation. Drug formulation manual where F_1 to F_3 formulation were made using of Carbopol-934 (F_4 to F_6) formulation were made using the sodium alginate. Preparation of Paracetamol-Aspirin transdermal gel Carbopol-934 and sodium alginate. Carbopol-934 and sodium alginate gel was prepared by using 1.5g, 2.0g and 2.5g of Carbopol-934 and sodium alginate in 60 ml distilled water, to give a final concentration, with continuous mixing with the help of continuous stirring, until a homogenous gel formed. The gel was set aside for few minutes until the bubble disappeared. Paracetamol (1 g) and Aspirin (0.05 g) was dissolved in ethanol and was further mixed with 10 ml of PEG-400 until homogenous to form transdermal gel. 1 ml of rose water as perfume was further added to the formulated gel. Carbopol-934 transdermal gel was found to be suitable candidate as it provided better consistency, spreadability, pH, homogeneity without producing any skin irritation. The pH values of Carbopol-934 gel formulation (F_1 to F_3) and Sodium alginate gel formulation (F_4 to F_6) ranged from 5.3±0.13 to 7.0±0.62 to avoid the risk of irritation after skin application. Spreadability of Carbopol-934 gel was found to be formulation F_3 (S=95.9) is good as compared to other formulation of Carbopol-934 and sodium alginate formulation, in which Carbopol-934 and PEG-400, were used as surfactant. After the produced gels were set in the container, they were all visually inspected to determine their homogeneity. They underwent examinations to check for aggregates and to see how they looked. All transdermal gel formulations show excellent homogeneity and lack of lumps.

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Conflict of Interest

None declared.

References

1. Laxmi RJ, Karthikeyan R, Babu PS, Babu RN. Formulation and evaluation of antipsoriatic gel using natural excipients. Journal of Acute Disease. 2013 Jan 1;2(2):115-21.
2. Shrestha S, Pokhrel S, Sharma S, Manandhar M, Alam I. Formulation and evaluation of topical microemulgel loaded with terbinafine hcl microemulsion. Int. J. Pharm. Sci. Res. 2017 Nov 1;26:4716-23.
3. Rasool BK, Abu-Gharbieh E, Fahmy S, Saad H, Khan S. Development and evaluation of ibuprofen transdermal gel formulations. Tropical journal of pharmaceutical research. 2010;9(4).
4. Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions: a review of the literature. Drugs. 1998 Nov;56:783-99.
5. McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol–a review. British journal of clinical pharmacology. 2018 Oct;84(10):2218-30.
6. https://www.tandfonline.com/doi/epdf/10.1080/20786190.2019.1610228?needAccess=true&role=button [Accessed on 20-09-2023]
7. Al-Alsadoon LH, AL-Saffar MT, Taqa GA. Comparative antinociceptive effect of aspirin and aspirin nanoparticles in semisolid formulae in mice. Iraqi Journal of Veterinary Sciences. 2021 Jul 1;35(3):535-9.
8. Zheng Y, Ouyang WQ, Wei YP, Syed SF, Hao CS, Wang BZ, Shang YH. Effects of Carbopol® 934 proportion on nanoemulsion gel for topical and transdermal drug delivery: A skin permeation study. International journal of nanomedicine. 2016 Nov 10:5971-87.
9. https://books.google.co.in/books?hl=en&lr=&id=dHL8DwAAQBAJ&oi=fnd&pg=PA3&dq=related:TLICjoOjzewJ:scholar.google.com/&ots=LXr3TOb2g-&sig=0AHcG4ks9TZ25D09xSv-maNUY9M#v=onepage&q&f=false [Accessed on 23-09-2023]
10. Rupal J, Kaushal J, Mallikarjuna SC, Dipti P. Preparation and evaluation of topical gel of valdecoxib. International Journal of Pharmaceutical Sciences and Drug Research. 2010;2(1):51-4.
11. Patel H, Panchal MS, Shah S, Vadalia KR. Formulation and evaluation of transdermal gel of sildenafil citrate. Int J Pharm Res Allied Sci. 2012 Mar 5;1(3):103-8.