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Treatment of Acne vulgaris with Adaplane-Benzoyl Peroxide Topical Gel Formulation and Control and the Effects of Treatment Psychology

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Abstract: Binary vulgaris is a very common disease among adolescents. Due to the effects it has on people's faces, it can impose many social and psychological costs on patients, so the treatment of this disease in addition to a health need is a social necessity. It is psychological. Therefore, in this study, Adapalene 0.1% and benzoyl peroxide 2.5% in a gel formulation were formulated for the first time in IRAN to guarantee better results and increase patients' acceptance of these two drugs at the same time. In the first stage, several formulations will be prepared using various jellies, which contain both benzoyl peroxide and adapalene, as well as other compounds such as hemoquantum, protective, etc. In the second stage, the various formulations prepared will be tested for physicochemical control. Control tests include determining the amount of active ingredient, checking for release simultaneously with the manufacture of the products, accelerated stability tests will be performed on the formulation to select the desired formulation based on the results of the control tests. In this work, we made eighty formulations, of which three formulations had the best physical and functional stability. Among them, la formulation was determined as the superior formulation and various physicochemical and microbial tests were performed on this formulation, all of which will confirm the superior product production method.
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Keywords: Acne treatment, adapalene topical gel control, benzoyl peroxide, vulgaris

1. Introduction

The skin is one of the most important organs in the body in terms of both weight, surface and physiology. After skeletal muscles, it is the heaviest (5% of the total body weight) and after the lungs (considering the level of their alveoli) it is the widest (2500 cm2) body-building organ (Adrangi, 1990). The skin weight is around 4.8 kg for men with average height and weight and 2.3 kg for women. In this calculation, subcutaneous fat tissue is not considered (Adrangi, 1990). Skin thickness is very variable and varies depending on various factors such as age, sex, individual fluctuations, heredity, occupation, race, etc. But on average it fluctuates between 0.7-4 mm (Barwaq, 1956). The pH of the skin is acidic and often in the range of 5-6-2-4 (Adrangi, 1990).

Acne vulgaris is a polymorphic and multifactorial inflammatory disease of the pelvic sebaceous follicles in the skin that timely and early treatment can prevent scarring, reduce the patient's cosmetic and psychological effects. Although a youth-related disease, it often persists as a problem into middle age. Due to its lipophilic properties, adapalene has selective adsorption into the pilobasse unit and plays an important role in anti-acne activity. Also, due to low percutaneous absorption, the risk of teratogenicity seems to be low (Tabiwat et al., 2006). It is also resistant to oxidation by benzoyl peroxide (Conley, 2002; Percy, 2003). Despite the existence of several treatments for this disease, the recurrence rate is relatively high, and most treatments have their own side effects (Klum, 1972; Logan, 2007). Topical retinoid, especially tretinoin, play an important role in the treatment of inflammatory and comedonal acne. By comparing new and synthetic derivatives of this group of drugs such as adapalene with older drugs in this group such as tretinoin, it is possible to identify a more effective drug with fewer side effects and to treat mild to moderate acne (Zhu et al, 2001).

In a recent study, 35% of women and 20% of men in their 30s had acne, while 26% of women and 12% of men in their 40s still had acne (Silverberg, 2001). It is very large (Smith, 2008). Psychological problems such as depression, anxiety, social exclusion, and even suicide are more likely to occur (Smith, 2007). With increasing pressure, the ruptured comedonal wall of creatine and immunogenic sebum are expelled and inflammation develops (Groekger, 2012). Propionibacterium acne and its interaction with the innate immune system % 0.1 and benzoyl peroxide

2.5% together in a gel formulation will be formulated for the first time in Kosher to achieve better results and increase patients' acceptance of the concomitant use of these two drugs.

Research method

Gel: It is a semi-solid system that is rich in liquid phase and is obtained by dispersing some gel-forming solids in a liquid phase. Gels are a key component. Like other dispersed systems, colloids are composed of two dispersed and continuous phases. And their difference with real solutions and dispersed systems with large particles such as suspensions and emulsions are related to the particle size of the dispersed phase. Dispersed phase particles in colloidal systems are at least between 10- 100 angstroms and at least a few microns. When the continuous phase of a gel is rich in liquid, the product is called a gel, and when the continuous phase contains a small concentration of solvent, it is called a dry gel.

Materials used in gel formulations

Gelling agents, tragacanth, sodium alginate, pectin, gelatin, starch, sodium carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose.

Common methods of preparing gels:

Hydration: In this method, the gel-forming material in the dispersed phase, which is usually a liquid solvent, turns into a gel over time due to the absorption of the swollen liquid from the tuberculous state.Like tragacanth, to accelerate this action, it is possible to stir the dispersed phase or heat it, creating transverse bridges by the action of chemical reactions. In these methods, by creating hydrogen bonds and other chemical bonds, active groups and other agents in different polymers of the gel are obtained.

For example, changing the pH in carbomers causes ionization of polymeric agents and gel formation, or importing some canyons, such as calcium in sodium alginate, form a gel by bonding between polymer chains.

Temperature changes: This method is effective in preparing some gels. In this case, by decreasing or increasing the temperature alternately, the polymer chains with iodine cross-links are given, which leads to the formation of a flexible coil and a gel

Materials used:

- Carbomer 940 prepared from Death Factory
- Ethanol prepared from the death plant
- Profit generated by Death Company
- Methanol provided by Death Company
- Tri ethanol Amin prepared from Death Company
- Acetonitrile prepared from Death Company
- Tetrahydrofuran prepared by Death Company
- Edetate sodium prepared by Razg company
- Adapalene provided by ran box / India death company
- Benzoyl peroxide from crystal / Italia The device used

❖ One-piece digital scale with weighing accuracy of 0.01 grams and maximum weighing 300 grams made by sartorious factory in Germany

❖ One-cup analytical scale with weighing accuracy and 0.0001 grams and maximum weighing 160 grams made by sartorious factory in Germany

❖ Simultaneously adjustable electric from 50 to 1400 rpm made by Iran Azma Teb factory

❖ High performance liquid spectrophotometer and chromatography device (GAM 321)

❖ Vacuum pump COM711a

❖ Model 4020 with adjustable speed

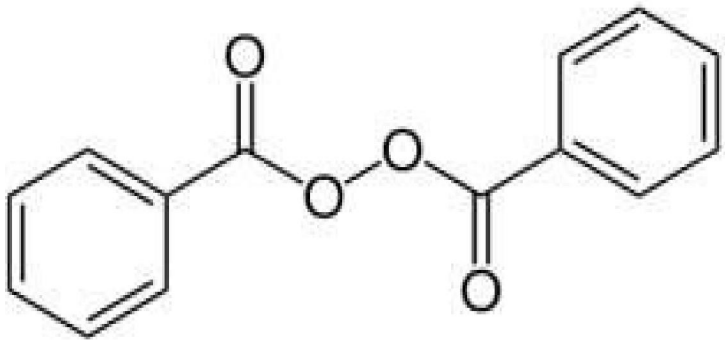
❖ pH meter

❖ Other equipment used in this work includes

❖ Human - Jujube balloon - Jujube pipette - Glass funnel - Glass vial of glass - Spanol - Distribution cell - Whatman filter paper - pH paper - Cellulose membrane

Adapalene from the third generation of retinoids has a mechanism similar to terinopine. Adapalene, like tretinoin, reduces the symptoms of acne vulgaris by normalizing the differentiation of follicular epithelial cells and their keratinization to prevent the formation of microcomodone. However, unlike tretinoin, adapalene binds selectively and specifically to some nuclear retinoic acid receptors. With this specific binding, the differentiation of keratinocytes increases without inducing epidermal hyperplasia and without any severe stimulation. Adapalene also helps reduce cell-mediated inflammation.

Indications
FDA-approved use
Treat mild to moderate acne vulgaris
Treatment of severe acne vulgaris (as a combination therapy) Off-label use
Keratospilar treatment Benzoyl peroxide:



Benzoyl peroxide

C_14 H_10 O_4: Molecular formula
242.23 g mol-1 Molar mass 9436-0: -CAS number
The mechanism of action:
Antibacterial effect (by releasing free radicals at the site of bacterial accumulation) Anti-inflammatory effect
Keratolytic effect

Microbiological test

This test is performed to ensure the absence of pathogenic microbes and the quorum of non-pathogenic microbes that may have been finalized during manufacture or through raw materials. In order to count the total number of live microorganisms in the product according to USP, 10 grams of the final product containing the active ingredient is poured under a laminar hood in a 100-cc jute balloon and then in order to neutralize the preservative effect and also to neutralize the alcohol in the gel base. It has antimicrobial properties; dilution method is used.

For this purpose, we dilute 10 grams of the final product containing the active ingredient in a 100-gallon balloon with phosphate buffer. As a result, a dilution of 10% (-1) is obtained. In the next step, we take 1 cc of this solution and add 9 cc of phosphate buffer to it. As a result, a dilution of 10% (-2) is obtained, then this work continues until it reaches a dilution of 10% (-4). Then we prepare 4 plates from each test tube.

To prepare each pilot, take 1 cc of the contents of each test tube and pour it on a plate, then add 20 cc of the desired medium to it, then place the SDA plates, which are 8 pieces, in a greenhouse at a temperature of 25 ° C and place for 14 days and place 8 TSA plates in a 35 ° C oven for 72 hours (29).

After the specified time, the number of colonies grown in each plate was counted and finally the total number of living microorganisms in the plant was calculated using the following formula.

Number of colonies * Dilution factor photo = number of living microorganisms per gram of product.

Basic formulation

To start the work, the base was made. In addition to the gels, which are not stable in hard gels and without which it is not possible to make gels, three materials of water, ethanol and propylene glycol were used. To build a base, you need to know how much of each of the above items to include in the formulation. Therefore, in order to prepare different formulations and compare them with others, and finally to select the best formulation for making adapalene-benzoyl peroxide gel, a

ternary diagram was used. The main advantage of using a ternary diagram is the systematic study of all points of the diagram and the introduction of the results obtained without the need for multiple tables and also the determination of one or more areas with different properties.

The ternary diagram was drawn as an equilateral triangle, each side of which represents one of the components used in the formulation.

Therefore, the effect of three variables on the products can be investigated simultaneously. All sides of the triangle are evenly spaced. This division can be clockwise or counterclockwise.

All the points marked on the sides according to Figure (1) are connected by drawing lines that are drawn parallel to each side of the triangle. In this way, each point that is created represents a formulation. To find the percentage of the components of each point on the diagram, draw lines parallel to the sides of the triangle from the corresponding point in the direction of the arrows to intersect the opposite side. The intersections of the sides of the triangle contain only one compound. But if the minimum value or

percentage of each compound on the diagram is not zero, the vertices of the triangle would also contain all three compounds. The diagram shown in the figure is based on three hypothetical materials A, B, C, each of which is divided into 10% intervals and the method of finding each of these three materials related to the X points is specified on it.

Making the base: To prepare the desired gel, a suitable base must be selected. What makes a base acceptable are features such as transparency, good non-stick consistency, easy and smooth spread on the skin surface and no skin irritation. If these are confirmed, it is time to add the active ingredient. After the product is approved in terms of appearance according to the above, then tests are performed to release the active ingredient from the gel base and its skin absorption. As we know, the main component in making gels are jellies.

Different jellies are used in the preparation of gels with different percentages. Depending on which jelly is used, the percentage used in the formulation will be different. To prepare the base for adapalene gel. In this method, after determining the percentage of materials used to dilute, first, 940 carbomer was weighed and poured into humans, then the water required for the formulation was added to the carbomer. To dissolve the polymer in water, an electric stirrer was used with the installation of a propeller stirrer. If the bubble swells too much, reduce the circumference of the device to eliminate the bubbles. After ensuring that the carbomer is dissolved in water and creating a clear solution, first ethanol and then propylene glycol were added as it may When adding ethanol, the solution is sprayed around. The device is reduced to 200 rpm, then ethanol and then glycerin are added to the contents inside the human and then mixed for 5 minutes. In this case, an acidic solution is obtained to form an onion gel by adding an alkaline substance. In an acidic environment, a small number of carboxia groups are ionized carbomers, and by adding base, more of them are ionized, and electrostatic forces between the charged regions cause molecular expansion and gel formation. For this purpose, t-ethanolamine was used. When adding triethanolamine, the device was set to the lowest rotation speed.

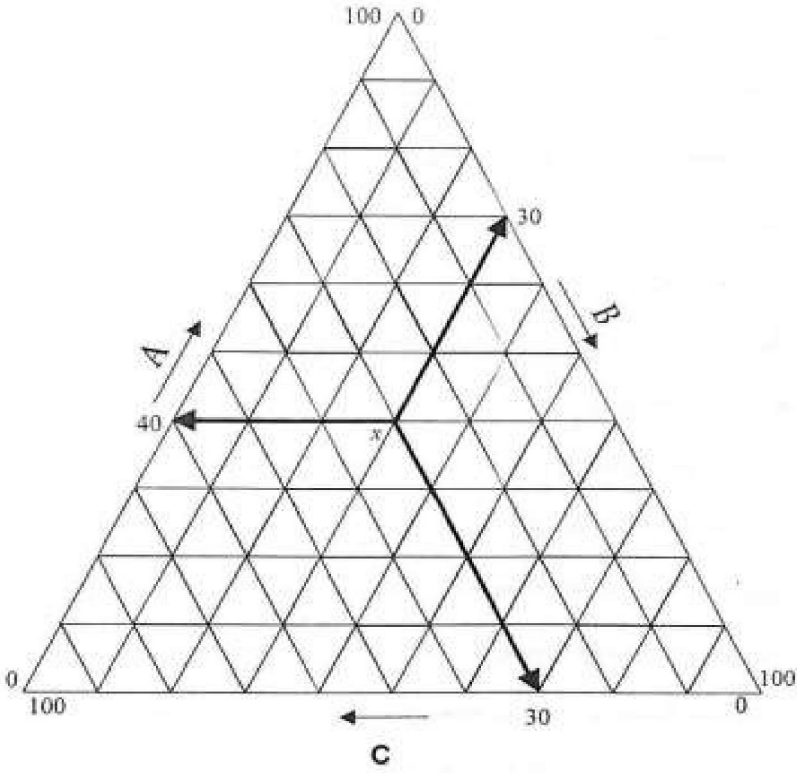


Figure 2: Ternary diagram used in the preparation of adapalene-benzoyl peroxide gel

Table 1: Ratio of materials used in the formulations obtained from the ternary diagram

	PG	Ethanol	water
1	10	10	80
2	10	20	70
3	10	30	60
4	10	40	50
5	10	50	40
6	10	60	30
7	10	70	20
8	20	80	10
9	20	10	70
10	20	20	60
11	20	30	50
12	20	40	40
13	20	50	30
14	20	60	20
15	20	70	10
16	30	10	60
17	30	20	50
18	30	30	40
19	30	40	30
20	30	50	20
21	30	60	10
22	40	10	50
23	40	20	40
24	40	30	30
25	40	40	20
26	40	50	10
27	50	10	40
28	50	20	30
29	50	30	20
30	60	40	10
31	60	10	30
32	60	20	20
33	60	30	10
34	70	10	20
35	70	20	10
36	80	10	10

Expand the ternary diagram in the desired area in order to achieve superior formulations:

After adding the active ingredient to the appropriate bases prepared with Cobomer 940, in order to study more accurately and achieve acceptable formulations, the diagram was expanded in a transparent area. The new diagram was divided into 5% intervals and the result was 45 formulations. And all the resulting formulations were prepared by adding the active ingredient. Among them, a formulation was selected that was superior to other formulations in terms of appearance characteristics such as consistency, transparency, non-irritation of the post and non-adhesion and no crusting when spreading on the skin.

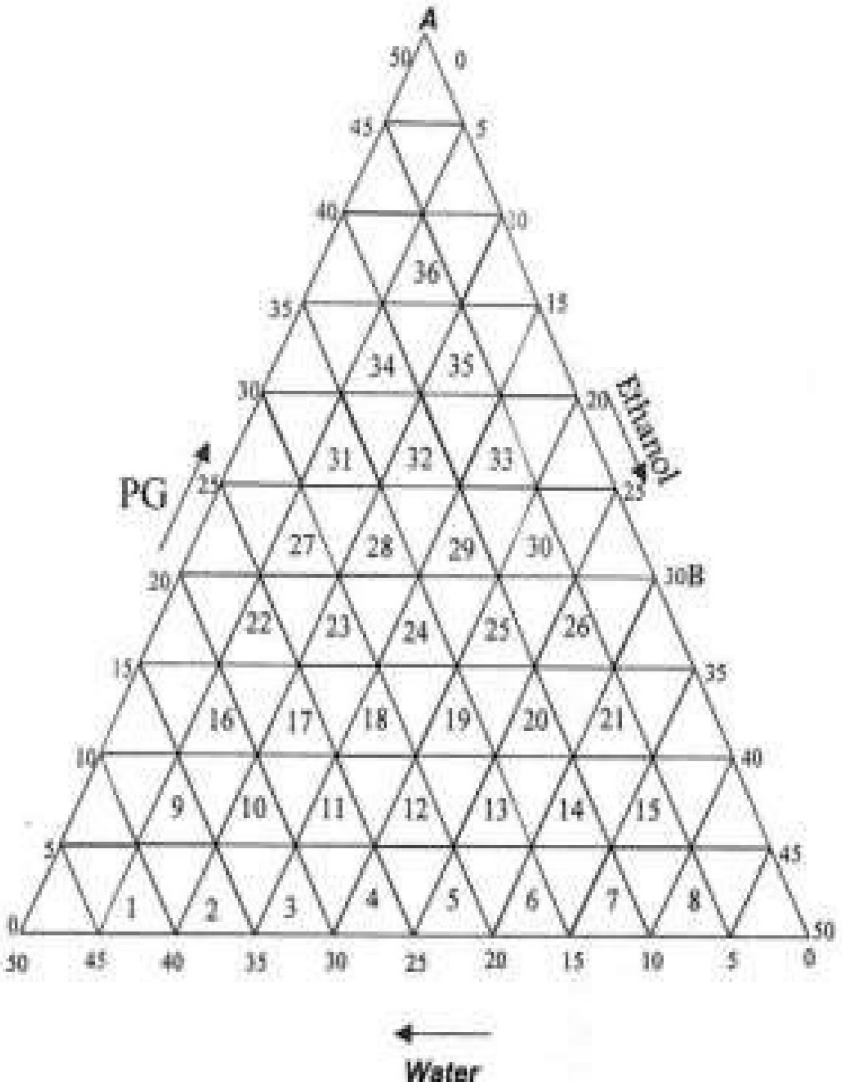


Figure 3: Ternary diagram to examine formulations containing 940 carbomer

Table 2: The ratio used in the formulations obtained from the ternary diagram

	PG	Ethanol	water
37	40	10	50
38	40	15	45
39	40	20	40
40	40	25	35
41	40	30	30
42	40	35	25
43	40	40	20
44	40	45	15
45	40	50	10
46	45	10	45
47	45	15	40
48	45	20	35
49	45	25	30
50	45	30	35
51	45	35	30
52	45	30	25
53	45	35	20
54	50	40	15
55	50	10	35
56	50	15	30
57	50	20	25
58	50	25	20
59	50	35	15
60	50	40	10
61	60	10	35
62	60	15	30
63	60	20	25
64	60	25	20
65	60	30	15
66	60	35	10
67	60	10	30
68	60	15	25
70	60	20	20
71	60	25	15
72	65	30	10
73	65	10	25
74	65	15	20
75	65	20	15
76	70	25	20
77	70	10	15
78	70	15	10
79	75	20	15
80	75	15	10

At the end of making these formulations, by examining all the formulations, we will reach the superior formulation, which we will discuss in the conclusion section.

Control experiments performed on adapalene-benzoyl peroxide gel

1. Stability test of physical properties
2. pH measurement

3. Spread test on the skin
4. Heat and cold cycle test
5. Rheology test
6. Determining the amount of active substance in the gel by HPLC method
7. Test the release of the active substance in vitro
8. Microbial control test

Stability tests of physical properties

Prepare samples of the selected formulation in the amount of 100 g and fill and package these samples in glass vials and place them at temperatures of 25, 4 and 40 ° C for 6 months and measure it in terms of color, viscosity and we considered two-phases.

pH measurement

To perform this test, first prepare a solution of the gel with a strength of 10% and then the pH electrode. After washing with distilled water, we put the meter in this solution and repeat this process three times, and then the standard and average deviation results will be taken. A normal pH range between 5-5.6 will be acceptable.

Skin spread test:

In this test, we put 0.5 g of gel on the skin of the back of the hand and spread it gently with the middle of the finger, and we repeated this three times. If conditions such as fragmentation during application, viscosity, excessive slipperiness, formation of inflexible and brittle film on the skin and scaling of the gel on the skin of the formulation are rejected.

Heat and cold cycle test

This test was performed to evaluate the stability of the product in terms of apparent stability and no biphasic at different temperatures. For this test, a sample of the gel was prepared and poured into three clear glass vials, and the vial was first placed in a refrigerator at 4 ° C for 24 hours, followed by 24 hours at room temperature at 25 ° C, and finally in the third 24 hours. We put at a temperature of 40 ° C and repeated this cycle for four periods and then we examined the product in terms of appearance characteristics and the absence of two phases.

Determining viscosity and examining rheological behavior

In this test, a Brook field rheometer model DV-III connected to the cone & plate system of cp-42 and an angle of 1.565 degrees was used to investigate the rheological behavior and determine the final fermentation viscosity of the prepared la prepared. To perform this test, we prepare three samples of the selected la formulation Then 1.5 g of the sample was placed in our space between the con & plate and the range of 0.3- 200mpm and the temperature of 23.9 shear stress were measured against different shear rates applied by the viscometer.Then from the ss obtained with pa unit against different SR applied with the unit rheograms related to the formulation were drawn using excel software and using the resulting rheogram first the type of rheological behavior and then the viscosity of the formulation in Pascal unit were determined.

Test to determine the amount of active ingredient in the gel

The method of choice for this test is the HPLC method because it has a high accuracy.

Table 3: Chromatographic conditions

Column type	4.6 mim* 25 cm hypersil BDS Column contains packing c18
Detector wavelength	325 nm
Flow rate	1.0 ml per minute
Volum of injection	20 ml
Coulumn oven temperature	30 ° C

Mobile phase

We prepared a mobile phase of 500 cc for this purpose.

Acetonitril, Tetrahydrofuran. purfild water, Trifluoroacetic acid (TFAA) in the ratio of 43:36:21:0.02v/v

Standard solution

Weigh 4 mg of adapalene and 10 mg of benzoyl peroxide and transfer to a 100CC flask, add about 70CC of the mobile phase, sonicate the solution, and finally reach 100 volumes.

Drug release test

The basis of this research is the release of the drug from the gel base and its part in the receptor phase, in which two important points are important.

1. Determine the appropriate environment for the test, which must be selected in such a way that it can dissolve the drug.
2. Establishing a sink environment is the most important factor in examining the drug release process. That is, the amount of receptor phase should be such that if all the material in the product is released and enters the receptor phase, the concentration of the active substance in the receptor phase does not reach the saturation limit and is equal to and less than 0.1 of its saturation concentrations.

In this experiment, we considered the base medium as phosphate buffer, but due to the fact that benzoyl peroxide has very low solubility in this buffer, we placed about 11% of the base medium in tetrahydrofuran, which has a 1: 1 solubility with benzoyl peroxide. In this experiment, a release test was performed using cellulose membranes. In this test, the cellulose membrane is cut to a size of 10 cm and soaked in the base solution for 24 hours. Use a syringe to insert the gel into the membrane. Two grams of gel is inserted into the membrane with a syringe. Then we completely closed it with a clamp and inserted it into the receiver phase by connecting it to the base.

Which is immersed in solution. We placed the human containing the receptor phase on a magnetic stirrer and adjust its circumference so that no eddy current is created, and the membrane remains fixed in the receptor phase. The results of the release test and the determination of the amount of active ingredient are given along with the diagrams.

Microbiological test

This test is performed to ensure the absence of pathogenic microbes and the quorum of non-pathogenic microbes, which may have been finalized during manufacture or through raw materials in the product. In order to count the total number of living microorganisms in the product, according to USP, 10 grams of the final product containing the active ingredient is poured under a laminar hood in a 100 cc balloon and then to neutralize the preservative effect and also to neutralize the alcohol in the base. Gel that has antimicrobial properties, dilution method is used. For this purpose, we diluted 10 grams of the final product containing the active ingredient in a 100-gallon balloon with phosphate buffer.

To prepare each plate, take 1 cc of the contents of each test tube and pour it into the plate and then add 20 cc of the desired medium to it. Then we put 8 SDA plates in the greenhouse at 25 ° C for 14 days and 8 TSA plates in the greenhouse at 35 ° C for 72 hours. After the specified period of time, the number of colonies grown in each plate was counted and finally the total number of living microorganisms in the plant was calculated using the following formula.

Number of colonies * Dilution factor photo = number of living microorganisms per gram of product

Conclusion

The purpose of this article is to formulate Adapalene-Benzoyl peroxide topical gel for the treatment and control of acne vulgaris and to evaluate the quality and quantity of the product. In the form of gel, compared to similar compounds in the form of ointments and creams, we decided to formulate this combination for the first time in the country.

Due to limited facilities on a laboratory scale, one of our problems in preparing this formulation was dispersing benzoyl peroxide in the gel base, which we solved by micronizing benzoyl peroxide and dispersing it in the base. The addition of dimethicone was able to greatly improve the appearance of the final product, while to solve the problem of non-aging of benzoyl peroxide, formulations with a higher percentage of water were inevitably chosen. Fortunately, we faced such a problem with Adapalene. We did not have good solubility in our gel base.

For the gel base, we used 940 carbomer in different concentrations, which obtained the best result at a concentration of 0.6. Examination of appearance properties (color, odor, transparency, appearance strength), viscosity and pH of the final product, confirmed our product. The mentioned formulation was also examined in terms of heat and cold Siegel test, which was completely confirmed.

To determine the amount of car, we used the HPLC method to check whether the amount of car in the final product is in the range of 110-90 or not? This test also confirmed the accuracy of our final product. Overall, the experiments performed in the laboratory environment were completely satisfactory to us and completely confirmed our product.

Suggestions for future work

According to the points observed during the study and research to complete the research process of the final formulation and complete assurance of the

efficiency of this product is recommended for future work:

- Study of periodic stability of the product and study of the effect of environmental factors on the stability of the product and subsequently determine its exact expiration date.

Extensive clinical studies to confirm the effectiveness of this type of product and ensure no side effects.

- Comparing the efficiency of this product in comparing similar foreign products Ale Scale up the present formulation for its industrial production.

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