IJPC

INTERNATIONAL JOURNAL OF PHARMACEUTICAL COMPOUNDING | NOVEMBER | DECEMBER 2024

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Development of A Topical Curcumin Gel for Skin Burn Regeneration

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Abstract

Topical treatment of burn wounds in all stages of burns plays an important role in the course and outcome of the acute period of burn injury, the patient's recovery time, and the development of infectious complications. Curcumin is considered a promising raw material in dermatology practice due to its accelerated wound-healing properties. However, as a result of the studies, it became clear that curcumin-based topical gel drug form for the treatment of burns has not been developed. In this study, we developed a new composition of the gel form for the treatment of burn wounds and its qualitative parameters were identified by Raman spectroscopy. A series of curcumin-containing gel formulations were prepared and evaluated based on their consistency, homogeneity, stability, and curcumin concentration, with the objective of identifying the optimal formulation. Drug kinetics were studied using diffusion methods. It has been demonstrated that a stable and pharmacologically active gel containing curcumin can be created, which has the potential for use in the clinical treatment of burn wounds.

Introduction

According to the World Health Organization, burns are the most common cause of death, accounting for approximately 180,000 patients each year. Non-fatal burns are a major source of morbidity, require long hospital stays, and often result in incapacitation and disability.[1]

Since gels have a number of advantages due to their local and resorption effect, they can compete with other types of semi-solid drugs in the treatment of infected wounds, burns, dermatitis of various etiologies, frostbite, dry skin, and joint pain. The ability to include various substances in the composition of gels and ease of use compared to other types of drugs is of great importance. Gels have a pH value close to the pH value of the skin, are easy to manufacture, do not clog skin pores, are easy to apply, and are evenly distributed.[2]

Curcuma longa L. belongs to the *Zingiberaceae* family, and its main biologically active substances are curcumin (diferuloylmethane), desmethoxycurcumin, and bisdemethoxycurcumin. *Curcuma longa L.* contains 0.2% to 5.4% curcumin. It also contains 4-14% essential oil, turmerone, allanthone and zingiberone, starch, and resin. Curcumin is considered a promising active pharmaceutical ingredient widely used in dermatological practice.[3,4,5,6]

Materials and Methods

The curcumin was purchased from Sigma-Aldrich Chemical Co. All other chemical products used in the experiments were obtained from the Laboratory of the Center for Pharmacy and Innovation at the Institute of Pharmaceutical Education and Research. Vaseline 8009-03-8, Lanolin 8006-54-0, Glycerin 56-81-5, Carbomer 9003-01-4, PEO 400, PEO 25322-68-3, MC 9004-67-5, Aerosil 7631-86-9, Sea buckthorn oil 225234-03-7, Nipagin 99-76-3, Nipazol 94-13-3. All the chemical products and bases used were of analytic purity grade.

PREPARATION OF CURCUMIN-BASED TOPICAL APPLICATIONS

Taking into account the physio-chemical properties of the bases, 5 different gel samples (MC 6%, Carbomer 1,5%, Aerosil 8%, Vaselin and lanolin 90:10, PEG 400 AND PEG 1500 45:35) were prepared (TABLE 1).

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TABLE 1.

AMOUNTS OF CURCUMIN AND EXCIPIENTS USED TO PREPARE (G/100G) GEL SAMPLES.

SAMPLES	CURCUMIN	VASELINE	LANOLIN	GLYCERIN	CARBOMER	0,1 N NaOH	PEO 400	PEO 1500	MC
S1	1	90	10	-	-	-	-	-	-
S2	1	-	-	20	-	-	45	35	-
S3	1	-	-	10	1,5	5 gtt.	-	-	-
S4	1	-	-	19	-	-	-	-	6
S5	1	-	-	-	-	-	-	-	-

TABLE 1 CONTINUED.

AMOUNTS OF CURCUMIN AND EXCIPIENTS USED TO PREPARE (G/100G) GEL SAMPLES.

SAMPLES	AEROSIL	AQUAE PURIFICATAE	SEA BUCKTHORN OIL	NIPAGINN	NIPAZOL	TOTAL
S1	-	q.s.	-	0,1	-	100 g
S2	-	-	-	-	-	100 g
S3		q.s.	10	-	0,1	100 g
S4	-	q.s.	-	0,1	-	100 g
S5	8	q.s.	-	0,1	-	100 g

Then curcumin was added to the prepared base with the addition of preservatives. In some samples, an emulsifier was added and mixed thoroughly until a uniform mass was formed. The fact that curcumin has a characteristic aromatic spice smell did not make it necessary to add corrigents to it. Prepared samples were packed in glass containers (100g) labeled "Neutral glass-3" with wide, rubber caps.[7,8,9] The technological scheme of the gel was developed (**FIGURE 1**).

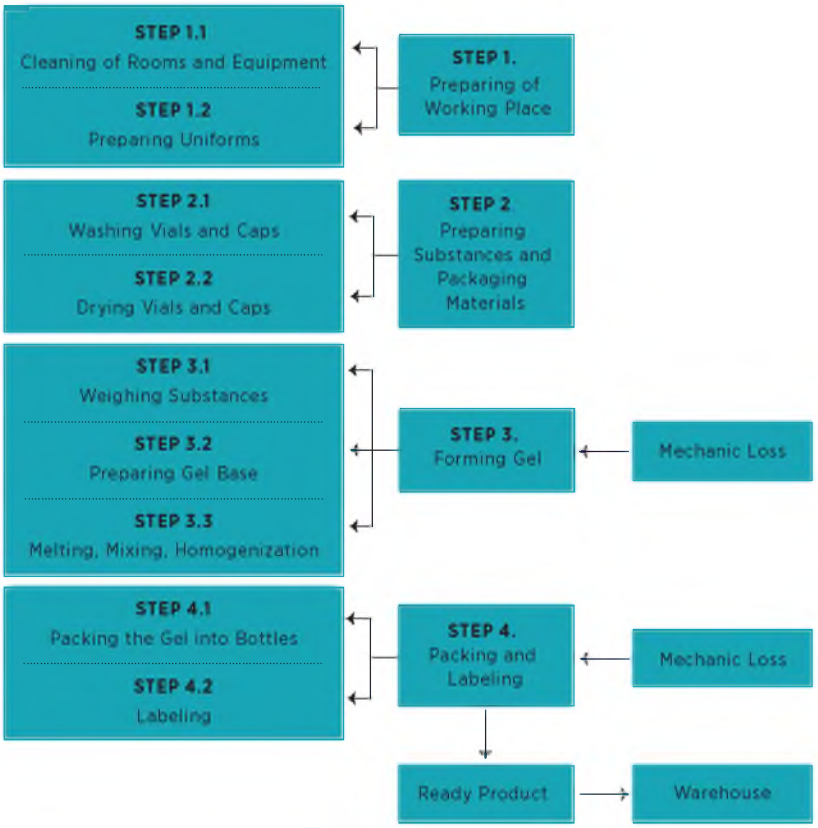
METHODS OF ANALYZING QUALITATIVE PARAMETERS

Appearance. The prepared samples were determined by their color, smell, the degree of application to the skin (easy, difficult).

Homogeneity. For analyzing uniformity, 4 samples of 0.2-0.3 g of were spread on 2 glasses. A cover glass was placed on top and pressed until it formed a circle with a diameter of 2 cm. When seen with the naked eye at a distance of 30 cm, visible particles were detected.

FIGURE 1.

PRODUCTION PROCESS FOR CURCUMIN GELS.



Determination of colloid stability was determined by centrifugation. The colloid was considered stable if separation into layers was not observed after centrifugation in the test tubes containing the samples. If sedimentation or delamination was observed in one sample, the experiment was repeated once again with new samples. Samples were taken from 5 g in a TsUM-1 centrifuge at 1500 rpm. Separation into layers was observed after centrifugation for 5 min.

TABLE 2.

RESULTS OF PHYSICAL EVALUATION FOR 5 TESTED CURCUMIN COMPOSITIONS S1-S5. COMPOSITION S3 MET THE REQUIREMENTS FOR ALL INDICATORS OF AN OPTIMAL GEL FORMULA AND WAS SELECTED FOR FURTHER STUDIES.

SAMPLES	VISUAL EVALUATION	CENTRIFUGATION STABILITY (5 MIN - 1500 RPM)	*THERMAL STABILITY	pH
S1	Yellow, visible particles, easy to apply	No phase separation	No phase separation	6.75
S2	Yellow, dense consistency, difficult to apply	No phase separation	Phase separated	6.60
S3	Yellow, uniform consistency, easy to apply	No phase separation	No phase separation	6.65
S4	Yellow, uniform consistency, difficult to apply	Phase separated	Phase separated	6.65
S5	Yellow, uniform consistency, easy to apply	Phase separated	Phase separated	6.55

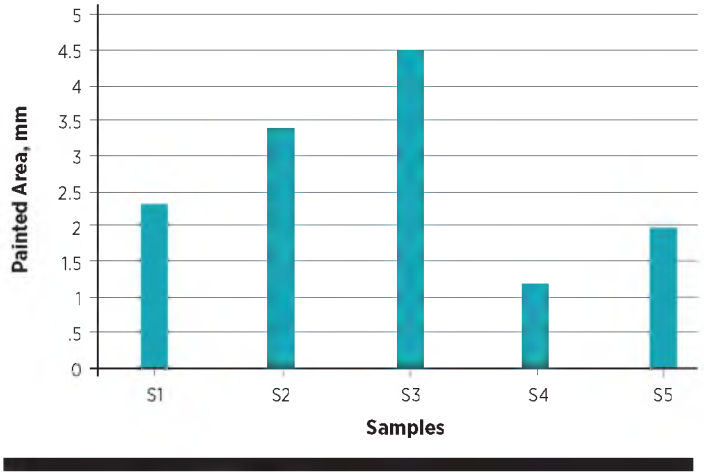
Determination of thermostability. 5-6 test tubes containing 6-10 ml of samples were placed in a thermostat at a temperature of 40-45°C for 7 days. After the specified time, these samples were placed in a refrigerator at a temperature of 10-12°C for 7 days. Then these samples were kept at room temperature for 3 days. Stability was determined visually: the sample was considered stable if there was no separation into layers in any of the test tubes.

Determination of pH value. The experiments were carried out on a Mettler Toledo pH meter (Schwerzenbach, Switzerland). The temperature condition for pH measurement was 23.6°C

Study of the release kinetics of drugs from the gel. The release kinetics of biologically active substances from the gel was studied using agar gel diffusion method. First, 30 ml of 2% agar-agar gel was prepared. To do this, 0.6 g of agar was placed in a container, purified water at room temperature was poured over it and left to boil for 30 minutes. After boiling for 1-2 minutes, the volume was brought up to 30 ml with water. 1 ml of 1% iron (III) chloride indicator was added to the cooled agar gel, mixed and poured in warm condition into 5 Petri dishes. Then left for 2 days. A well was made in the center of the agar gel using a cylinder with a diameter of 8 mm, and 0.3 g of the curcumin gel (S_1, S_2, S_3, S_4, S_5) under study was drawn onto it. The level of the red color formed around the wells was measured after 2 days using a millimeter scale in 5 Petri dishes.

FIGURE 2.

DYNAMICS OF THE RELEASE OF BIOLOGICALLY ACTIVE SUBSTANCES FROM DIFFERENT BASES IN DIFFUSION METHOD. THE MAXIMUM DIFFUSION DISTANCE WAS OBSERVED FROM CURCUMIN SAMPLE S3 INDICATING FASTER CURCUMIN RELEASE RATE FROM S3 COMPARED TO OTHER FORMULATIONS.



Raman spectroscopy. The analyses on Raman spectrometer were performed on a model R-532 ("Enhanced Spectroscopy" USA) with a spectral range from 100 to 6000 cm^{-1}, the spectral resolution of 5-8 cm^{-1}, laser wavelength 532 nm, laser power 50 mW, linear CCD array, pixel number 3648, focal length 75 mm, entrance aperture 20-30 microns, holographic diffraction grating 1800 lines/mm. The measurements were conducted at room temperature.[10,11]

Determining the viscosity of the gel. It is known that many substances in the preparation of semi-solid drugs have complex rheological properties, and their viscosity can change depending on conditions (time, pressure, deformation, temperature). In particular, the type of base, composition, concentration, and stability have a significant effect on the rheological properties of biopharmaceutical preparations. Rheological properties of substances are important at every stage of industrial production, from the selection of content and development of technology to the processing of waste products. Taking into account the above, the viscosity index of curcumin-based gel was studied in a viscometer named HAAKE Viscotester 7 plus

FIGURE 3.

RAMAN SPECTRUM OF CURCUMIN REFERENCE STANDARD.

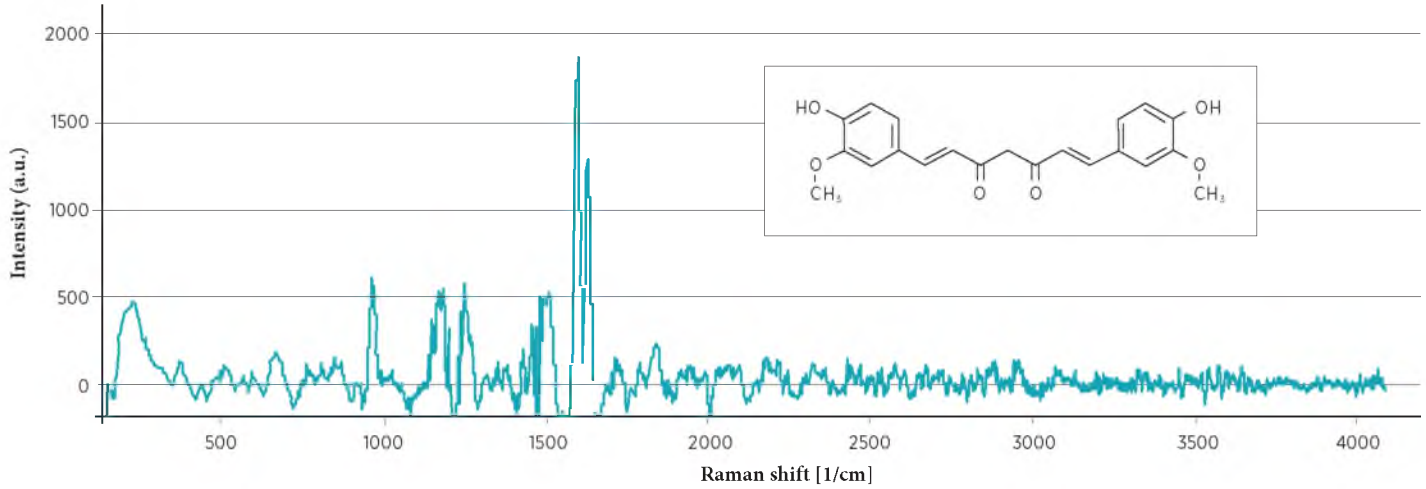
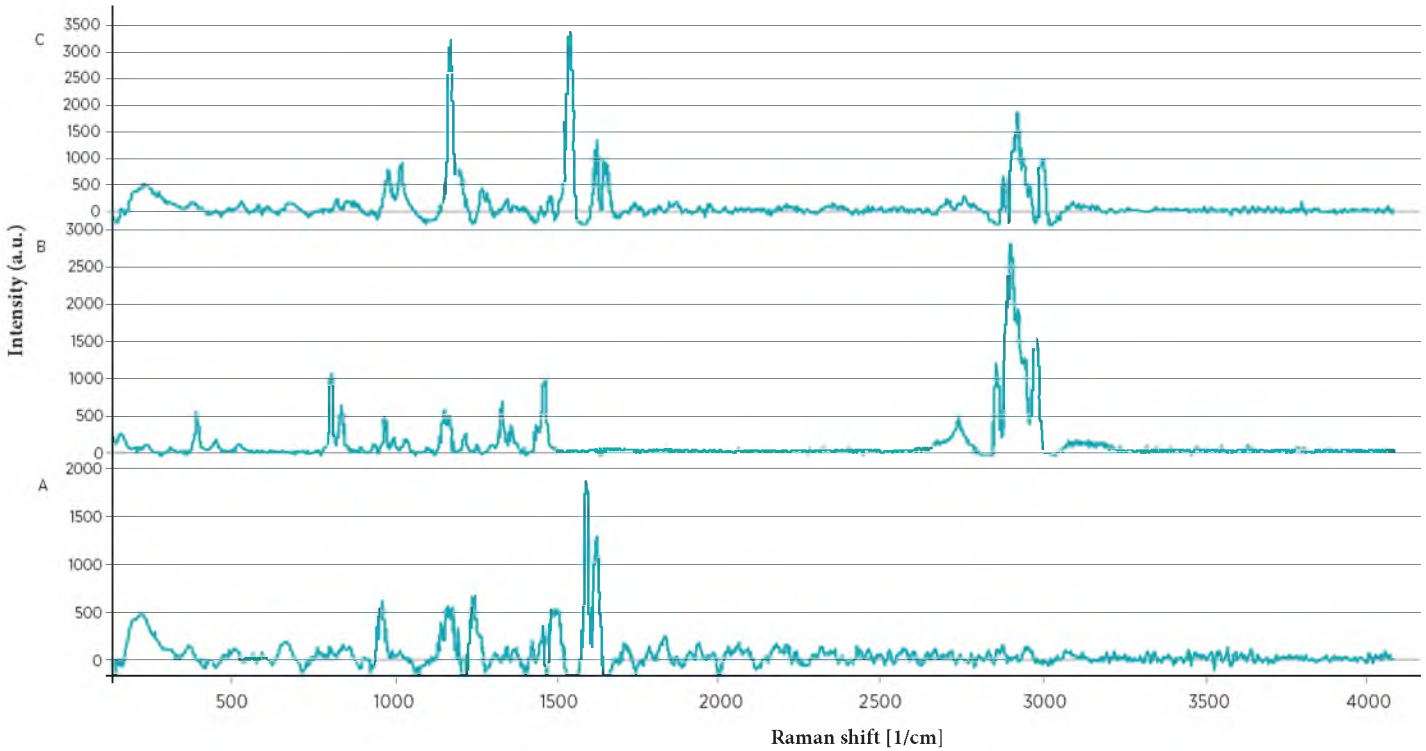


FIGURE 4.

RAMAN SPECTRA OF A) CURCUMIN REFERENCE STANDARD, B) BLANK S3 GEL WITHOUT CURCUMIN, C) S3 CURCUMIN GEL. MAJOR PEAKS ASSOCIATED WITH CURCUMIN WERE OBSERVED IN S3 SPECTRUM (C), BUT WERE NOT PRESENT IN SPECTRUM FOR THE BLANK GEL (B).



(Therma scientific, Spain) working on the Brookfield principle with spindle number 4 at 25°C, the room temperature was 23.3°C, and the humidity was 36.5%. Viscosity was measured at various speeds of the spindle ranging from 5 to 100 revolutions per minute (rpm). Thirty milliliters of the prepared sample was taken in 100 ml beaker and the viscosity was measured without the guardleg. In order to compare the same process, 1% of the carbomer gel was carried out. Before starting the measurements, the viscometer level was adjusted using the two leveling screws on the base. The rheological behavior of the polimer (Carbomer gel 1%) and the effect of curcumin on them (Curcumin gel 1%) studied and compared based on the plotted rheograms for the data generated. Viscosity is a function of shear rate. The speed of the spindle was used instead of the actual shear rate to plot the graphs. Plots of rpm versus apparent viscosity were drawn and analyzed in the TABLE 4.

Determining the dynamics of gel dehydration. Gels lose their moisture content and dry up as a result of storage, which is one of their main disadvantages. With this in mind, further studies focused on determining the dynamics of gel dehydration. For this, the 3rd gel sample was applied thinly on a glass plate with a surface area of 10 cm^2 and left at room temperature. Every 30 minutes, the gel mass was determined by measuring the decrease in weight. Based on the obtained results, the dynamics of gel dehydration is shown in FIGURE 5.

TABLE 3.

COMPARISON OF RAMAN SPECTRAL DATA OF CURCUMIN STANDARD AND CURCUMIN GEL FORMULATION S3. CHARACTERISTIC PEAKS OF CURCUMIN WERE OBSERVED IN THE GEL SAMPLE S3. THIS METHOD WILL BE VALIDATED FOR STABILITY-INDICATING ASSAY OF CURCUMIN IN THE FOLLOW UP STUDY.

FUNCTIONAL GROUPS	CURCUMIN STANDARD (CM^{-1})	S3 BLANK CARBOMER GEL (CM^{-1})	S3 CURCUMIN GEL (CM^{-1})
δ C-C	370	396	368
ν C-C skeletal	851	806, 837	837, 846
C-O-C symmetric	963		964
Carboxylic acid dimer		970	
ν C-C		1150, 1161	1154
$-CH_2$ twisting and rocking	1175		1182
C-O	1245	1215	1249
δ CH		1326	
$-CH_2$ wagging		1356	
$-CH_2$ scissoring	1457	1455	1457
δ $-CH_3$ asymmetric	1486, 1505		
CH – O ··· C=O			1518
Aromatic ring	1595		1597
ν C=C	1625		1627
C=O	1716, 1835		1836
ν $-CH_2$		2879, 2899	2867, 2881
ν -CH		2918, 2954	2920, 2956

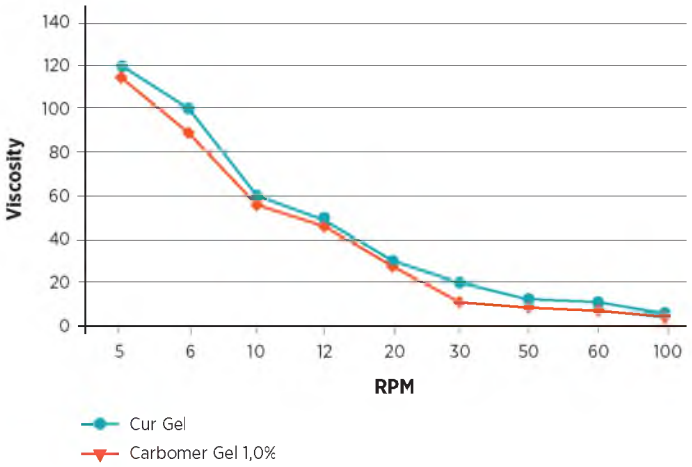
Results and Discussion

At the initial stage of the research, parameters such as appearance, color, application to the skin, and uniformity of the gel were determined and it was found that the samples № 2, 4 were not homogeneous and formed a consistency that was difficult to apply to the skin. On determining the size of the particles in the gel samples it became clear that the sample 1 contained visible particles. At the same time, when the colloidal and thermal stability of the prepared samples was checked, separation into layers was observed in samples 2, 4, and 5, and they were excluded from the experiments. Based on the obtained conclusions, sample 3 was selected for further research (TABLE 2).

Study of the release kinetics of drugs from the gel. In method, the maximum release of medicinal substances was determined in 3 sample. (FIGURE 2).

TABLE 4.

DETERMINING THE RHEOLOGICAL BEHAVIOR OF THE POLIMER (CARBOMER GEL 1%) AND THE EFFECT OF CURCUMIN ON THEM (CURCUMIN GEL 1%).



RESULTS ON RAMAN MEASUREMENT OF CURCUMIN IN THE SAMPLE

In the Raman spectrum of the curcumin standard sample, the characteristic combination scattering lines are located in the range of 950-1800 cm^{-1}. The aromatic ring vibration at 1595 cm^{-1}, ν C=C valence vibration at 1625 cm^{-1}, ν C=O medium intensity scattering lines of the carbonyl group at 1716 cm^{-1}. Also, the C-O bond belonging to the phenol group is located at 1245 cm^{-1}, the non-intensive valence vibrations of the C-O-C bond are located at 963 cm^{-1}, and the asymmetric deformation vibrations of the $-CH_3$ group are located at 1486 cm^{-1} (FIGURE 3, 4).

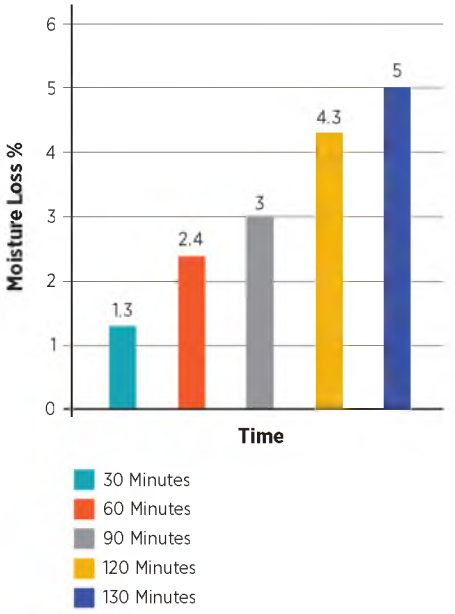
According to spectra and table data, it is obvious that the characteristic peaks of curcumin were preserved in the gel formulation (TABLE 3). This method showed that it is possible to evaluate the quality of the curcumin gel drug form .

During the study of the viscosity properties of the gel prepared on the basis of curcumin and intended for the treatment of burns, it was found that, the optimal technology of bases, gel-forming agents and other auxiliary substances was selected, and curcumin had no significant effect on the rheological properties of the curcumin semi-solid drug at different pressures (TABLE 4).

According to the results of the experiments, the number 3 gel sample lost 1.3% moisture in 30 minutes, 2.4% in 60 minutes, 3% in 90 minutes, 4.3% in 120 minutes, and 5% in 130 minutes. (FIGURE 5).

FIGURE 5.

DETERMINING THE DYNAMICS OF GEL DEHYDRATION. THE AMOUNT OF WEIGHT LOSS (%) DUE TO MOISTURE EVAPORATION FROM S3 CURCUMIN GEL OVER 130 MIN (SEE TEXT FOR THE DEHYDRATION CONDITIONS).



Conclusion

According to the above methods, the 3rd sample was found to be positive. The conducted experiments showed that the color and smell of the obtained gel did not change, separation into layers was not observed, and the active substance and bases in the gel were determined to be proportional. During the study of the viscosity properties of the gel prepared on the basis of curcumin and intended for the treatment of burns, it was found that, the optimal technology of bases, gel-forming agents and other auxiliary substances was selected. It can be said that the mass loss of the gel did not exceed the required time limits. In subsequent studies, the decision was made to conduct further pharmacological research.

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