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PRELIMINARY EVALUATION OF DICLOFENAC GEL AND EMULGEL FORMULATED USING BENTONITE AS A GELLING AGENT

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In this work, a bentonite from Maghnia (northwestern Algeria) was used as a gelling agent in gel and emulgel formulations. The percentage of Na-bentonite in the formulations was fixed at 5%. The physical appearance of the formulated gel and emulgel was characterized before determining their pH, viscosity and swelling index. A rheological analysis demonstrated the characteristic shear thinning and viscoelastic behavior of the formulations using thixotropy. Stability studies showed that the physical appearance and rheological properties of the prepared gel and emulgel remained unchanged having been stored for 3 months. An FTIR study proved that the drug and excipients are compatible with each other. The prepared formulations exhibited acceptable physical properties as well as levels of homogeneity, consistency and viscosity. The pH fell within an acceptable range of 6.40-6.80.

Keywords: bentonite, formulation, gel, emulgel, rheology, diclofenac

1. Introduction

Bentonites, formed by the weathering of volcanic tuff and ash, consist mainly of montmorillonite, containing varying amounts of other minerals like quartz, calcium and sodium feldspar. They are a type of clay mineral that is composed mainly of montmorillonite, which is a layered silicate mineral and its chemical formula is $(Na,Ca)0.33(Al,Mg)2Si_4O_{10}(OH)_2$ x nH_2O [1].

In general, bentonites are classified into two types: Na-bentonite, which has a high swelling capacity, and Ca-bentonite, which is a non-swelling clay and forms a colloid very quickly in water [2]. Due to their exceptional rheological properties, bentonite suspensions are widely used in different industrial applications such as in pharmaceuticals [3]-[5]. This mineral also contains small amounts of other minerals such as feldspar, quartz and calcite. The composition of bentonite varies depending on the location and geological environment where it is found [2],[5]. Bentonite exhibits several unique properties that make it an attractive material in various applications. Some of the important properties of bentonite are as follows:

- Swelling: Bentonite can absorb water and swell up to several times its original size. This property is due to the presence of interlayer cations, which are exchanged with water molecules [1].
- Cation exchange capacity (CEC): Bentonite has a high CEC, which is a measure of its ability to exchange cations. This property makes it useful for removing impurities and contaminants from water as well as other liquids [1].
- Rheological properties: Bentonite exhibits thixotropic and plastic behavior, making it useful as a thickening agent and binder in various applications [1],[6].

Bentonite also exhibits good adsorption properties, rendering it useful for removing impurities and contaminants from pharmaceutical products. Furthermore, this mineral has several applications in the pharmaceutical industry. It is used as a more environmentally sustainable and inexpensive material. In recent years, based on its high retention capacity as well as swelling and colloidal properties, bentonite has been proposed as a useful material to modify drug delivery. Because of their swelling potential, clay minerals can be effectively used to delay (extended-release systems) drug release or even improve drug solubility. Zheng et al. investigated the interaction between ibuprofen and montmorillonite clay [4], while Park et al. studied the intercalation of donepezil, a well-known drug for treating Alzheimer's disease, in montmorillonite [7]. Other examples of drugs effectively carried by clays include nicotine and timolol [8]. Compared to all the clay

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Table 1: Composition of the two formulations - gel and emulgel

Ingredients	Emulgel (%w/w)	Gel (%w/w)
Diclofenac sodium	1.00	1.00
Propylene Glycol	5.00	5.00
Bentonite (4% Na)	5.00	5.00
Carbopol 940	0.25	0.25
Liquid Paraffin	7.50	-
Benzoic Acid	0.25	0.25
Purified water	q.s. to100%	q.s. to100%

minerals, montmorillonite has been extensively used in the pharmaceutical field [9].

Gels for dermatological use exhibit several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients and soluble or miscible in water.

Emulgels are emulsions, with either oil-in-water or water-in-oil high patient acceptability since they possess the previously mentioned advantages of both emulsions and gels. Therefore, they have been recently used to deliver various drugs to the skin [10]. The aim of this work was to create a gel and emulgel formulation using a bentonite modified in Algeria [5] as a gelling agent with a low quantity of Carbopol 940. The stability of this type of gelling agent was studied from the prepared gel, that is, an emulgel. Their organoleptic properties were investigated by visual aspect and microscopic analysis as well as the rheological properties of the prepared gel and emulgel evaluated over 3 months.

2. Experimental

2.1. Materials and methods

Bentonite was collected from Hammam Boughrara (Algeria) and provided by Bentol; benzoic acid, propylene glycol (PG) as well as diclofenac were purchased from Sigma-Aldrich; while Carbopol 940 and liquid paraffin were obtained from CLCM Labs.

2.2. Preparation of Na-bentonite and semi-solid formulations

Bentonite was activated using 4% Na_2CO_3 [5]. The semi-solid formulations were prepared with diclofenac sodium. Adequate preformulation studies were conducted in order to optimize the concentration of the excipients based on visual changes in their appearance, microscopic evaluations and any alterations to their physical characteristics prior to manufacturing the final formulations. The compositions of the final optimized formulations are shown in *Table 1*.

2.3. Manufacturing process of emulgel

The drug was dissolved in PG before being added to the aqueous phase. The oily phase was added to the aqueous phase and homogenized at 6000 rpm using a high shear homogenizer (HR-500D, FAITHFUL). The formulation was then cooled to room temperature while mixing continuously to form a smooth emulsion [10]. In addition, the gel portion was prepared by dispersing 5% bentonite in water at room temperature and mixing until a homogeneous dispersion was obtained before Carbopol 940 (0.25%) was added. The emulsion was then gently mixed with the gel in a 1:1 ratio to obtain the emulgel.

2.4. Manufacturing process of the gel

The gel formulation was made by slowly dispersing Bentonite in water while stirring continuously and allowing the dispersion to hydrate for 60 minutes before adding Carbopol 940 to form an ameliorate texture. The drug was dissolved in a suitable amount of PG before being transferred to the container and continuously stirred until a homogenous gel was produced [11].

2.5. Microscopic evaluation

A microscopic evaluation by polarized light microscopy was used to evaluate the formulations. A small amount of each product was placed on a glass slide and spread evenly using a coverslip. The formulations were observed under a bright-field microscope using a 40× objective and photomicrographs recorded using a HUND microscope (H 600 Wilo-Prax PL bino).

2.6. pH measurements

A pH meter (HI 2210 pH meter, HANNA, France) was calibrated using buffered standards of pH 4, 7 and 10. Approximately 10 g of each formulation was placed in a suitable container and tapped to remove entrapped air. The pH of all the formulations was recorded before washing the probe with deionized water and 70% v/v ethanol after each measurement.

2.7. Fourier-transform infrared analysis

The spectroscopic analysis was conducted using an IRAffinity-1S Fourier-transform infrared spectrometer (FTIR) equipped with a Shimadzu DLATGS (deuterated L-alanine doped triglycine sulfate)-type detector within the range of 4000-400cm^{-1} and a diamond cell to allow direct analysis.

2.8. Rheological characterization

The rheological behavior of the different formulations was evaluated by using a stress-controlled rheometer (HAAKE RheoStress 1). The equipment consisted of a

Table 2: Visual aspect of the gel and emulgel formulations

Formulation	Emulgel	Gel
Aspect	Homogenous	Homogenous
Microscopic examination	Stable	Stable
pH	6.40	6.80
Viscosity (cP)	42.454	35.121

multi-stage Peltier module and a 25 mm sandblasted parallel plate. In order to maintain the temperature of the formulations during the experiments at 32± 0.1 °C and prevent any possible evaporation, the measuring system was equipped with a standard TR9 spindle and a Thermo Haake P5 ultrathermostat to simulate skin temperature. All measurements were triplicated. For each test, approximately 0.5 g of a sample was placed on the lower plate before slowly lowering the upper plate to achieve the preset gap of 100 microns. In order to characterize their rheological behavior, each sample was subjected to a steady-state flow method (0.1–100 s^{-1}) to characterize their flow properties and obtain viscosity values at low (2.0 s^{-1}), medium (20.0 s^{-1}) and high (75.0 s^{-1}) shear rates. In addition, dynamic oscillatory tests can be used to evaluate the microstructure of a viscoelastic material. After identifying the linear viscoelastic region (LVR) by using the strain sweep for each formulation, a frequency sweep was performed over an angular frequency range of 0.1–100 rad/s in order to understand the viscoelastic nature of the formulations.

In order to determine the degree of water absorption, the samples were immersed in water at 37 °C. At scheduled time intervals, the samples were removed and weighed. Water absorption was calculated using the following equation:

$$Water\ absorption = (W_t - W_d)/W_d \quad (1),$$

where W_t (g) denotes the weight of the swollen sample at the immersion time t and W_d (g) represents the weight of the dry sample (initial sample). The measurements of all the samples were triplicated (*Figure 1*).

3. Results and discussion

3.1. Visual evaluation and pH measurement of the semi-solid formulations

The formulations shown in *Table 1* were evaluated based on their visual appearance (*Table 2*). The gel formulation was clear and homogenous, while its emulgel counterpart was translucent and homogenous in appearance (*Figure 2* and 3). The pH of the gel-like emulgel fell within the range of 6.40–6.80 which is considered acceptable to prevent any irritation when applied to the skin [9],[10],[12].

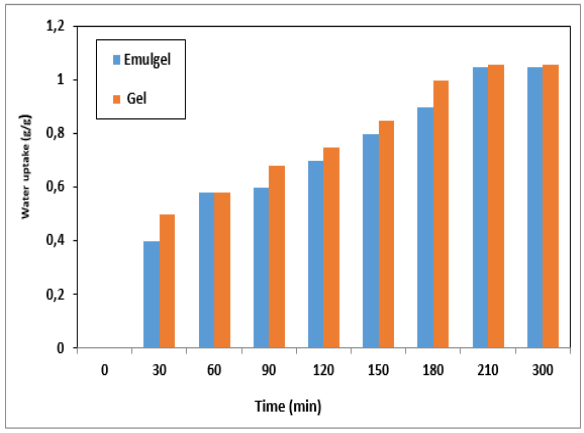

Figure 1: Water absorption of the gel and emulgel

Figure 2: Gel

Figure 3: Emulgel

3.2. Microscopic evaluation

The two formulations were evaluated under a microscope using a 40× objective. The microscopic pictures (*Figure 4*) of the gel formulation show that diclofenac was dissolved and no crystals of API visible. In the case of the emulgel formulation, typical globules were visible under the microscope but no crystals of the drug were present.

3.3. Rheological characterization

Understanding the rheology of the semi-solid formulation is important because it may have an impact

Table 3: Flow of the gel and emulgel formulations at low, medium and high shear rates

Shear rate (s^{-1})	Viscosity (cP)	
	Emulgel	Gel
Low at 2.0	42.352	29.188
Medium at 20.0	12.997	3430
High at 75.0	4352	1320

on the way the therapeutic agent is applied and delivered. Therefore, research was conducted to determine how different processing parameters or stressors affected the rheological characteristics of the semi-solid formulations [10],[13].

Flow curve (viscosity vs. shear rate)

As seen in *Table 3*, the viscosity of the emulgel was found to be higher. The two semi-solid formulations were found to be characteristically shear thinning and non-Newtonian as the shear rate increased. Therefore, at low shear rates, the formulations were highly viscous, representing its initial physical stability/firmness before use. As the shear rate was increased, the viscosity of the formulation quickly decreased, indicating its ease of spreadability upon application of the formulation topically [10].

Linear Viscoelastic Response

Figure 5 shows that the gel and emulgel formulations exhibited similar viscoelastic behavior when subjected to increasing strain with the storage modulus (G') greater than the loss modulus (G''). This shows that cohesive forces were heavily predominant in the microstructure of the formulations, facilitating easy application on the skin without any dripping off.

Thixotropy

Figures 6 and *7* show the entire rheograms (shear stress vs. shear rate) of the gel and emulgel formulations.

As seen in the figures, the gel and emulgel formulations exhibited shear-thinning behavior since the viscosity (the gradient of the curve) decreased as the shear rate increased. As the shear stress increases, the normally disordered molecules of the gelling material align their long axes in the direction of flow. Such an orientation reduces the internal resistance of the material, thereby decreasing the viscosity. The figures also indicate thixotropic behavior where the down curve was displaced with regard to the up curve, showing that at any shear rate on the down curve, a lower shear stress was observed than on the up curve. Therefore, a hysteresis loop formed between the two curves. Thixotropy, or time-dependent flow, occurs because the gel or emulgel formulations require a finite time to rebuild their original structures that break down as a result of continuous shear measurements. It is noteworthy that thixotropy is a desirable characteristic in pharmaceutical preparations, both in terms of engineering design and consumer application, in order to deliver an initially thick product

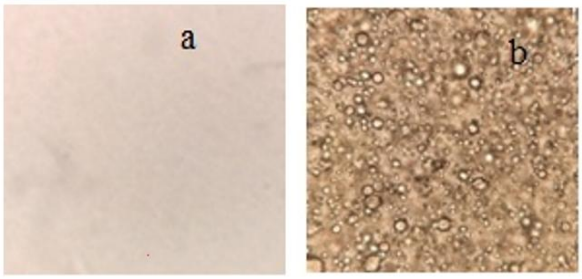

Figure 4: Microstructure of the gel (a) and emulgel (b)

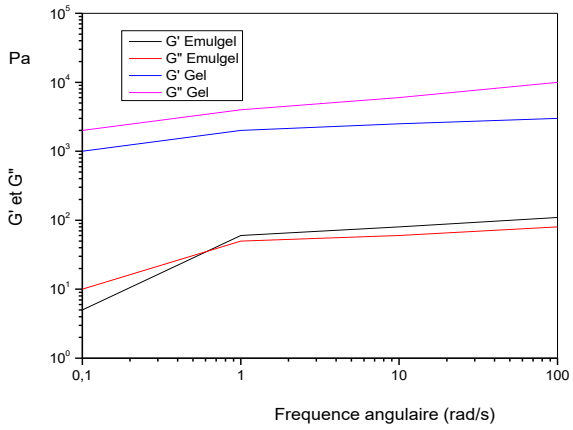

Figure 5: Linear viscoelastic response

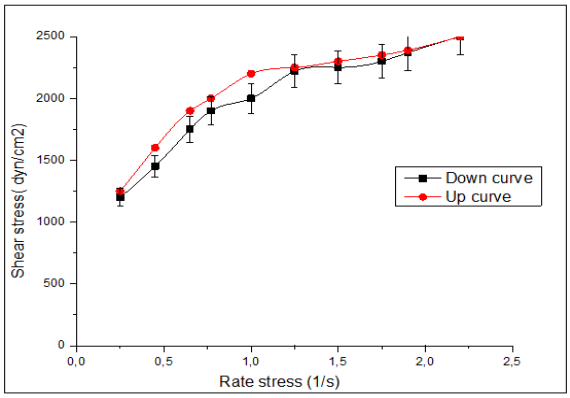

Figure 6: Rheogram of the gel formulation

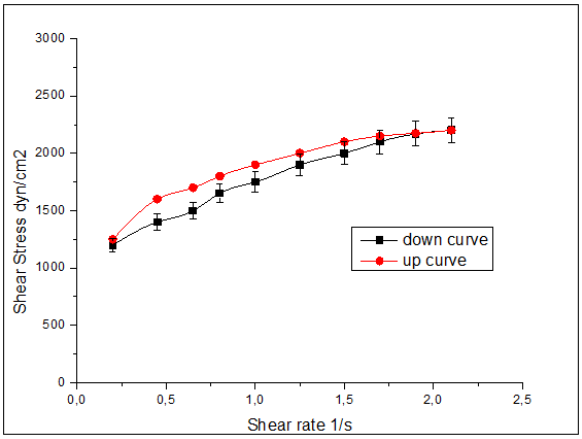

Figure 7: Rheogram of the emulgel formulation

as a thinner, easily spreadable material. These findings are in agreement with Mohamed Magdy who prepared a chlorphenesin emulgel using two types of the gel forming materials [12].

3.4. Stability of the studied formulations

The prepared formulations were found to be stable after having been stored for 3 months, during which no change was observed in their physical appearance, pH or rheological properties.

The swelling of the formulations was studied at pH 7.2 at room temperature. All the formulations exhibit almost 100% swelling. Although the gel swells slightly more than the emulgel, the difference is insignificant.

3.5. FTIR analysis

The FTIR spectra of the gel and emulgel formulations are shown in *Figure 8*. FTIR spectroscopy revealed that the various vibrations between the functional groups of the different bonds in the two formulations are similar. All the characteristic peaks exhibit vibrations due to varying functional groups that represent common components of the two formulations and indicate the absence of any overlap between the peaks.

The FTIR spectra of the formulations show a large peak at 3400 cm^{-1}, which is associated with the stretching of the O–H groups as well as hydrogen bonding. The peaks at 2933 and 2850 cm^{-1} can be attributed to CH–(17) stretching. The peak at 1730 cm^{-1} corresponds to C=O stretching. Therefore, the excipient and drug are compatible with each other in both formulations, moreover, the gel and emulgel formulations are stable [9].

4. Conclusions

By developing and evaluating emulgel and gel formulations, it was concluded that activated bentonite is a good vehicle for semi-solid formulations. Organoleptic and sensory analyses were performed with visual verification of their color, odor, appearance and texture. The averages of the results were calculated to determine the pH of the formulations. It was observed that the pH of the gel and emulgel formulations were within a range suitable for skin application. A rheological study revealed the thixotropic behavior of the gel and emulgel formulations. The semi-solid formulations with diclofenac sodium prepared in this study were found to be stable and exhibited characteristic rheological behavior, which was found to be favorable for topical application. In addition, bentonite modified in Algeria exhibited acceptable gelling properties and is a more environmentally sustainable as well as inexpensive material.

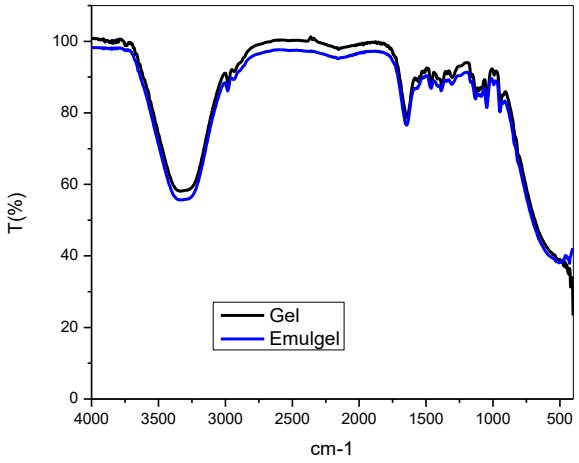

Figure 8: FTIR spectra of the gel and emulgel formulations

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