The Pharma Innovation Journal 2016; 5(4): 76-79

www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2016; 5(4): 76-79

www.thepharmajournal.com
Received: 08-02-2016
Accepted: 12-03-2016

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Rheological properties of emulgel formulations based on different gelling agent

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Abstract
This study was conducted to determine the viscoelastic properties and rheological characterization of some emulgel formulations that includes gelling agents from different groups: natural, synthetic and semi-synthetic. The first step of semisolid drugs development is a selection of appropriate base, thru the large range of bases an emulgel is one of most prefered. In case of pharmaceutical forms, emulgels are emulsions that are gelled by mixing with a gelling agent; they possess advantages of both emulsions and gels. Briefly, advantages of emulgels are ease of spreadability, convenience of viscosity and appearance and emollient effect. Gelling agent has a appreciable influence on rheological properties of emulgels. The prepared emulgels exhibited non-Newtonian shear thinning behavior with thixotropy. Four emulgels showed excellent stability as they demonstrated consistent rheological model under different treatment conditions.

Keywords: Rheological properties, emulgel, gelling agent, thixotropic

Introduction
Transdermal drug delivery via the skin is beneficial, because it avoids the risks associated with intravenous therapy and the inconveniences associated with varying gastric pH, emptying time, and hepatic metabolism [1]. This type of administration of drugs is not easy because of the impermeable nature of the skin. The stratum corneum, the outermost layer of the epidermis, is the essential permeability barrier that limits the passage of most compounds. Normally, the penetrant that is applied to the skin surface may trespass the stratum corneum through three pathways: via appendages or through transcellular or intercellular routes [2]. In fact, only small and lipophilic compounds are able to penetrate the stratum corneum; therefore, this poses a problem for cosmetic and cosmeceutical products: how to overcome the skin barrier and facilitate the active ingredients deep into skin where they can exhibit their functions [3].
This implies that either some new form of topical delivery that is both safe and practical or a delivery vehicle for systemic use must be developed. Both these approaches hold promise for both improved treatment of common problems and effective treatment of diseases for which there is now no adequate therapy. Much emphasis is placed on the efficacy of topically applied therapeutic agents and developing appropriate formulations (pharmaceuticals) to facilitate their delivery [4].
The type of topical formulation chosen in this study is an emulgel. Emulgels (emulsion gels) are a class of biphasic semi-solid formulation [5]. Currently, they are being tried for controlled delivery applications [6]. Due to the presence of both aqueous and non-aqueous phases, emulgels offer the capability of delivering both hydrophilic and lipophilic agents [7]. Though the emulgels are biphasic in nature, they are thermodynamically more stable as compared to emulsions. Due to the above-mentioned reasons, the emulgels provide the advantages of both emulsions (biphasic system) and gels (improved stability).
In recent years, emulgels have gained importance in topical drug delivery. Emulgels help to improve the penetration of the drugs into the systemic circulation through the skin and prevent first-pass metabolism. The drug passage through the stratum corneum in emulgels and microemulsion gels is based on conventional diffusion mechanism, but the surfactants and the fatty acids in oil phase, may also act as penetration enhancers and can cause the increased drug penetration and accumulation into the skin [8]. These properties of emulgels increase the bioavailability of the drugs. Also, an improved patient compliance has been reported due to the reduced dosing frequency [9].
The objective of this work was to compare rheological properties of emulgel formulation with different gelling agents for pharmaceutical and cosmetic usages. However, it was worth mentioning that most of the previous studies about emulgel used natural polysaccharides or synthetic polymers as gelling agents separately. Consequently, there is no relevant reports

about comparative studies of properties of emulgels with different type of gelling agents. That's why the main goal of this work was comparison of emulgels, which were prepared using various gelling agents: natural (guar gum), synthetic (Carbopol) and semi-synthetic (HEC).

Materials and Methods

Materials

The emulgel formulations were prepared according to our own prescription. They contain oil phase (Almond oil and Shea butter) with emulsifier MONTANOV 202 and water phase with gelling agents (HEC, Guar gum, Carbopol 980 NF). MONTANOV 202 was purchased by intermediate company from SEPPIC (France). HEC, Guar gum, Carbopol 980 NF, TEA were supplied from Sigma-Aldrich, (Germany). All other reagents obtained commercially were of analytical grade and used as received. Double distilled water was used throughout the study.

Preparation of formulations

Emulgels were prepared in two steps, by two methods. In step I, the gel phase was prepared; in step II, the gel phase was combined with the oily phase in order to give the final emulgel formulation. The proces of emulsification was carry out using different equipment. In one case we used Unguator® e/s, in another the PRO 250 rotor-stator homogenizer with the Speed Control Boxes.

The codes and ingredients of formulations F1–F6 are given in Table 1.

Table 1: Content of formulations (%)

Ingredient	Technological process					
	Unguator® e/s			PRO 250 rotor-stator homogenizer		
	F_1	F_2	F_3	F_4	F_5	F_6
Almond oil	15	15	15	15	15	15
Shea butter	5	5	5	5	5	5
MONTANOV 202	5	5	5	5	5	5
HEC	1	-	-	1	-	-
Guar gum	-	1,5	-	-	1,5	-
Carbopol 980 NF	-	-	0,3	-	-	0,3
Potassium sorbat	0,2	0,2	0,2	0,2	0,2	0,2
TEA	-	-	0,45	-	-	0,45
Water	to 100,0	to 100,0	to 100,0	to 100,0	to 100,0	to 100,0

Methods

Organoleptic controls

Organoleptic assessment. Particular features of the prepared emulgels, such as ease of spreading on the skin, ease of their absorption by the skin, leaving oily or non-oily sensation on the skin and washability of residual film of the emulgels were evaluated as 0 (unavailable), + (moderate), ++ (good), +++ (best) [10, 11]. In addition, general appearance, water dilution characteristics, homogeneity, odor, color and consistence of the formulations were evaluated [11].

pH measurements

The pH measurements were done at room temperature (24±1 °C). Samples were prepared by dilution of 1 gram of emulgel to 10 mL with purified water before the experiment. Measurements were taken in sextuplicates.

Viscosity measurements

The rheological properties of emulgel samples were determined using cone and plate Brookfield viscometer (using Brookfield Digital Rheometer Model DV-III, DV3T™ Rheometer, USA). About 0.5 g of the formula to be tested was applied to the plate and left for equilibrium, measurements were made at 20 °C (room temperature) and 32 °C (temperature of skin surface) at shear rates ranging from 0.4 to 400 s^{-1} corresponding to 0.2 to200 rpm with 10 s between each two successive speeds and then in a descending order. Measurements were taken in sextuplicates. The hysteresis loop between the upward and downward curve were studied. Also the apparent viscosity at 20 s^{-1} were determined from the rheograms [12].

Results and Discussions

Evaluation of the organoleptic properties of emulgel formulations F_1 – F_6 are presented in Table II. Formulations which were produ ced with synthetic and semi-synthetic gelling agents have white colour and emulgels with guar gum were creamy. All formulations didn't have oily feel on skin and good absorbed. Only emulgels with guar gum didn't have a good homogeneity. Emulgels F_1 and F_3 showed the best spreadability and homogeneity among the formulations.

According to the results of pH analysis presented in the same table, the range of pH of formulations was from 5.91 ± 0.025 to 6,94±0,031, which is considered acceptable for avoiding the risk of skin irritation.

Table II: Organoleptic controls and pH of prepared formulations

Control	F_1	F_2	F_3	F_4	F_5	F_6
Oily feel	0	0	0	0	0	0
Spreadability	+++	+	+++	++	+	+++
Ease of absorption	+++	+	+++	++	+	+++
Water dilution	++	+	++	++	+	++
Stickiness	+	+	++	+	+	++
Homogeneity	+++	0	+++	++	+	+++
Odor	+	+	+	+	+	+
Color[a]	W	C	W	W	C	W
pH	6,94±0,031	6,87±0,068	5,91±0,025	7,02±0,035	6,77±0,070	6,05±0,015

0 (unavailable), + (moderate), ++ (good), +++ (best) [a]C – Cream, W – White

A flow curve, viscosity versus shear rate, across a wide range of shear rates Newtonian flow is the simplest type, displaying as shear-independent viscosity while the material is sheared. Water and some low-molecular-weight mineral oils are typical examples of Newtonian fluids. Pseudo-plastic or shear thinning fluids display viscosity reduction while the shear rate increases. Typical examples of these are colloidal systems. The colloidal structure breaks down while shear rate increases, displaying reduced viscosity. Dilatant or shear thickening flow, in which viscosity increases with shear rate, is seldom encountered in the pharmaceutical and cosmetics fields [13].

Viscometry studies were carried out in order to investigate formulation flow properties and a type of gelling agent influences. The measurements (shear stress vs. shear rate) were performed at 20 °C, to simulate storage conditions, and at 32 °C in order to reproduce the skin application environment. The range of shear rate that was suggested in this study varied from 7,68 to 130,56 and was justify by the index of torque. But for formulation with guar gum this speed was too high and index of torque exceeded the limits, that's why the range of shear rate for formulations with gum was from 0,77 to 7,68 according to the limits of the torque index. Viscosity curves, reported in fig.1 and fig. 2, show that all formulations have non-Newtonian flow type.

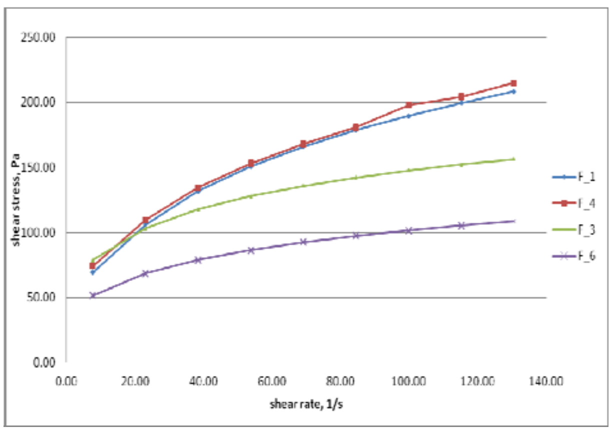

Fig 1: Plot of the shear stress (τ) as a function of the shear rate (γ) for the emulgels with Carbopol and HEC at 20 °C

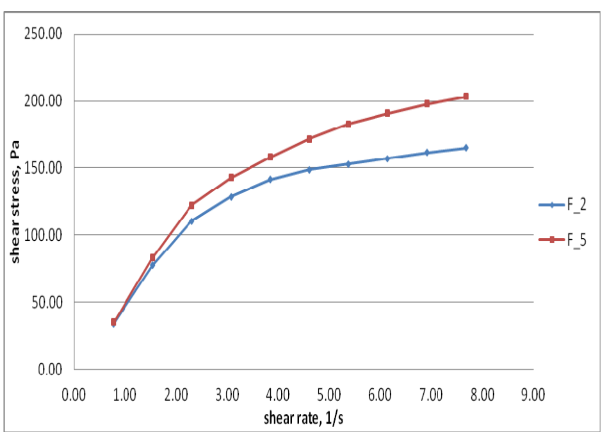

Fig 2: Plot of the shear stress (τ) as a function of the shear rate (γ) for the emulgels with Guar Gum at 20 °C

The data suggest that the formulation viscosity is mainly influenced by the proces of emulsification. Emulgels with guar gum (F_2 and F_5) and HEC (F_1 and F_4) show higher shear stress in a case of preparing using the PRO 250 rotor-stator homogenizer (F_4 and F_5), but generally it is so significantly. But for preparation with Carbopol (F_3 and F_6) the way of preparation has a significant impact.

The same conclusion for these formulations in investigations at the temperature 32 °C (fig. 3 and fig. 4)

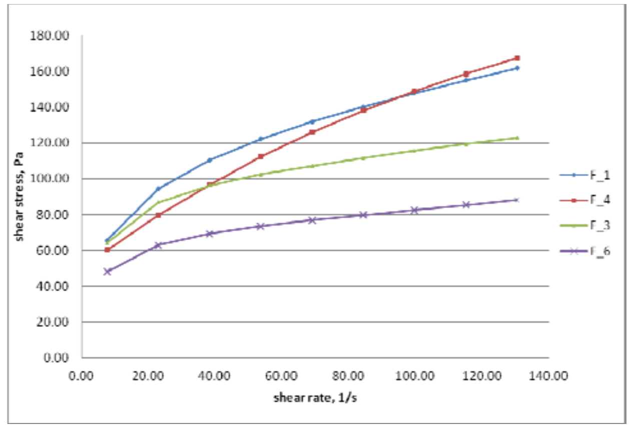

Fig 3: Plot of the shear stress (τ) as a function of the shear rate (γ) for the emulgels with Carbopol and HEC at 32 °C

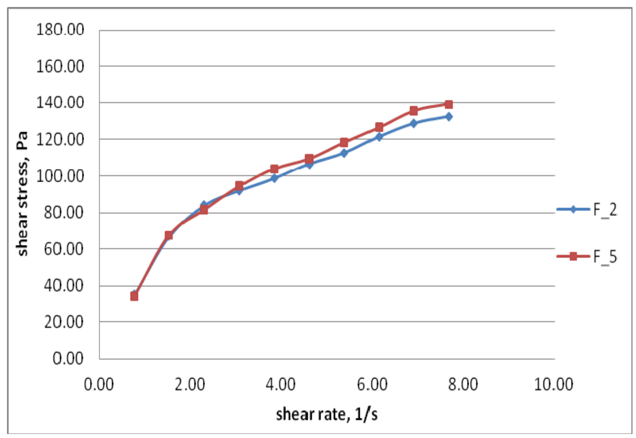

Fig 4: Plot of the shear stress (τ) as a function of the shear rate (γ) for the emulgels with Guar Gum at 32 °C

The next step of our rheological investigation was to discover the viscosity of preparing formulations. This investigation was care out in conditions of room temperature (20 °C) and at 32 °C.

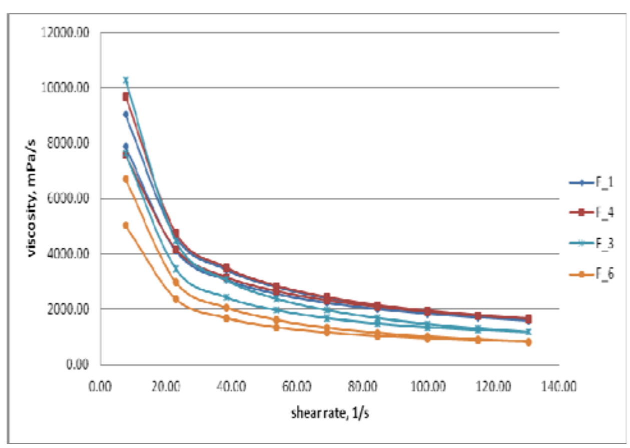

Fig 5: Plot of the viscosity (η) as a function of the shear rate (γ) for the emulgels with Carbopol and HEC at 20 °C

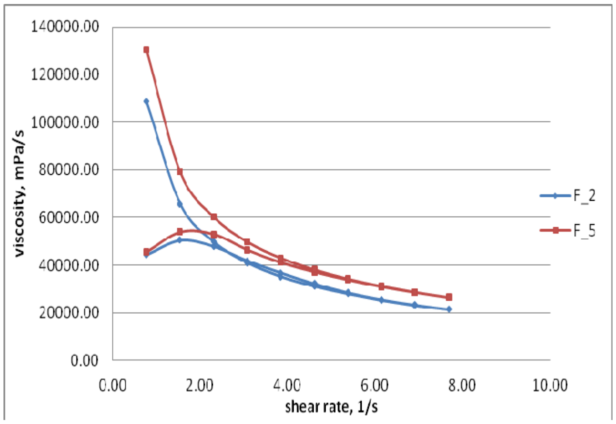

Fig 6: Plot of the viscosity (η) as a function of the shear rate (γ) for the emulgels with Guar Gum at 20 °C

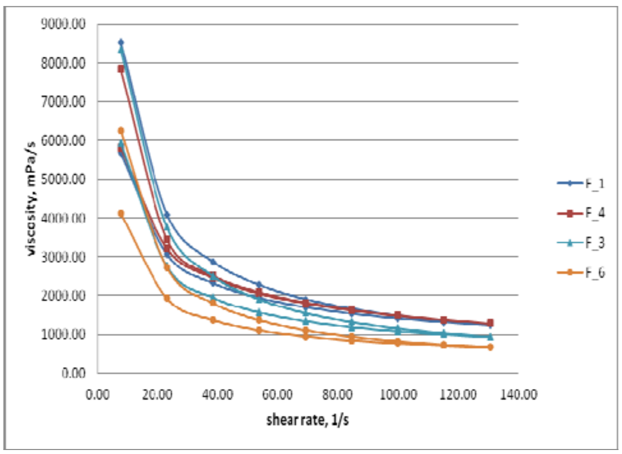

Fig 7: Plot of the viscosity (η) as a function of the shear rate (γ) for the emulgels with Carbopol and HEC at 32 °C

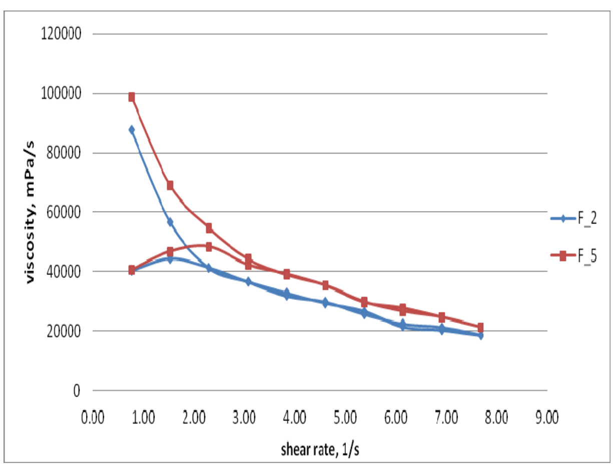

Fig 8: Plot of the viscosity (η) as a function of the shear rate (γ) for the emulgels with Guar Gum at 32 °C

Rheograms of emulgel formulations with Carbopol and HEC show good viscoelastical properties, which we observe at fig. 5 and fig. 7. All these formulations have possibility to return to their original state once the stress is removed. But for emulgels with guar gum we have different results, viscosity of these formulations are change a lot under the shear stress. In the case of viscosity we do not observe significant changes, depending on the technology of emulsification.

Conclusion

Organoleptic properties of formulations determined that better characteristics have emulges with Carbopol 980 NF (F_3) and HEC (F_1), which were preparing in Unguator® e/s.
As a general consideration, the changes in formulation viscosity were mainly attributed to the type of gelling agent and don't depend a lot of equipment which we use to make an emulsion. As expected, also the synthetic and semi synthetic polymer form a better formulations.

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