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(54) Title: PHARMACEUTICAL COMPOSITION, PROCESS FOR OBTAINING THE PHARMACEUTICAL COMPOSITION, USE OF A PHARMACEUTICALLY EFFECTIVE AMOUNT OF ANESTHETIC AND GELLING AGENTS, PRODUCT AND METHOD OF TREATMENT

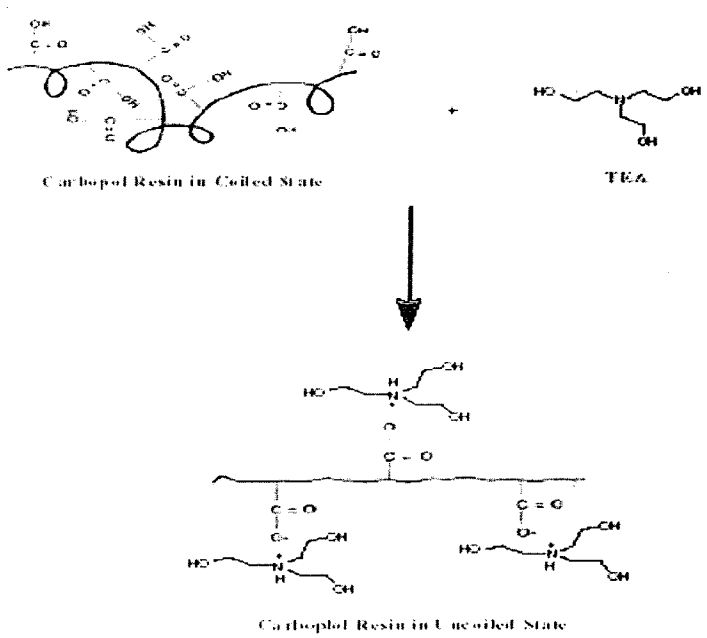

FIG. 1

(57) Abstract: The present invention refers to a pharmaceutical composition for a local anesthetic gel intended for topical use in dental procedures. The pharmaceutical composition comprises a pharmaceutically effective amount of at least one anesthetic and at least one gelling agent, said composition having a minimum viscosity of 30 Pa. s, when subjected to a temperature ranging from 5°C to 50°C. The subject invention allows a higher penetration of the anesthetic through a stable viscosity which maintains the drug for a longer time and at a higher concentration on the action site, increasing anesthesia time, reducing its toxicity, and restricting the action of the drug to the application site.

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Specification of Patent of Invention for **"PHARMACEUTICAL COMPOSITION, PROCESS FOR OBTAINING THE PHARMACEUTICAL COMPOSITION, USE OF A PHARMACEUTICALLY EFFECTIVE AMOUNT OF ANESTHETIC AND GELLING AGENTS, PRODUCT AND METHOD OF TREATMENT".**

Field of the Invention

The present invention refers to pharmaceutical compositions of local anesthetic gels which have stable viscosity when subjected to a temperature in the range of 5°C to 50°C, for topical application on buccal mucosa and intended for use in dental procedures.

Description of the prior art

Local anesthesia is the most commonly used method for pain control in dentistry. However, this is one of the most stressfull procedures in patients, especially due to the use of dental needles. Topical anesthesia is the main method used for minimizing the pain caused by puncture during the procedure of local anesthesia (Martin et al., Topical anaesthesia: differentiating the pharmacological and psychological contributions to efficacy – Anesth Prog. 1994).

Topical anesthesia has been shown a great efficacy in reducing the discomfort caused by the puncture in almost all cases, except for the palatal mucosa and in block

anesthesia (Meechan JG., Intra-oral topical anaesthetics: a review – J Dent. 2000; Meechan JG., Effective topical anaesthetic agents and techniques – Dent Clin North Am. 2002).

The efficacy of topical anesthesia depends on some factors, such as: anesthetic agent used, application time of the topical anesthetic, application site, needle diameter used, as well as the depth of the needle penetration (Meechan JG., Effective topical anaesthetic agents and techniques – Dent Clin North Am. 2002).

The most commonly used topical anesthetic is 20% benzocaine in pharmaceutical gel form, due to its fast time of action (30 seconds), acceptable taste, and the absence of systemic absorption (Priemosch et al., Comparison of topical EMLA 5% oral adhesive to 20% benzocaine on pain experienced during palatal anesthetic infiltration in children – Pediatr Dent. 2001).

Anesthetics belonging to the ester group, such as benzocaine and tetracaine, which are still being used as topical anesthetics in Dentistry, have a higher allergic potential than those belonging to the amide group (Meechan JG., Effective topical anaesthetic agents and techniques – Dent Clin North Am. 2002). The efficacy of benzocaine in minimizing pain caused by puncture in infiltration anesthesia in the anterior maxillary region and the palatal mucosa has already been shown (Rosa et al., Larrador MA. Clinical effectiveness of lidocaine and benzocaine

for topical anaesthesia – Anesth Prog. 1999; Nusstein et al., Effectiveness of 20% benzocaine as a topical anesthetic for intraoral injections. Anesth Prog. 2003). However, its efficacy as a topical anesthetic previously to the regional anesthesia of the inferior alveolar nerve block was not proven (Meechan JG., Effective topical anaesthetic agents and techniques – Dent Clin North Am. 2002).

In recent years, the euthectic mixture of two-based anesthetics, lidocaine- and prilocaine (EMLA® Astra Zeneca) has achieved a higher efficacy as compared to benzocaine and lidocaine (Vickers et al., Pulpal anaesthesia from an application of a eutectic topical anesthetic - Quintessence Intl.1993). The acronym EMLA (Euthectic Mixture of Local Anesthetics) designates a euthectic mixture of local anesthetics. This designation is given when the combination of agents (lidocaine and prilocaine) shows a lower melting point than shown by these substances in their isolated forms. Lidocaine, prilocaine, and the euthectic mixture have melting points of 69°C, 37°C, and 17°C, respectively. This property allows the anesthetic agent to remain in oil form at the temperature of the buccal cavity (37°C), causing an increase on the local absorption of the anesthetic agent (Vickers et al., Pulpal anaesthesia from an application of a esthetic topical anesthetic - Quintessence Intl.1993). EMLA has been developed approximately 20 years

ago for dermatological use and, in the last decade, has been tested for intraoral use.

Studies demonstrated the efficacy of EMLA in topical applications, allowing procedures such as periodontal instrumentation to be carried out (Svensson et al., Efficacy of a topical anesthetic on pain and unpleasantness during scaling of gingival pockets –Anesth Prog 1994; Perry et al., Effectiveness of a transmucosal lidocaine delivery system for local anesthesia during scaling and root planning – J Clin Periodontol 2005), in Dentistry (Vickers et al., Pulpal anaesthesia from an application of a euthetic topical anesthetic - Quintessence Intl.1993; Vickers et al., Pharmacokinetics of EMLA cream 5% application to oral mucosa – Anesth Prog 1997) and in some cases of extractions and biopsy (Taware et al., A bioadhesive delivery system as an alternative to infiltration anesthesia – Oral Surg Oral Med Oral Pathol Radiol Endod. 1997; Meechan., The use of EMLA for an intraoral soft-tissue biopsy in a needle phobic: a case report – Anesth Prog 2001). EMLA has also reduced the discomfort caused by the placement of clamps in absolute isolation used for carrying out restorative and endodontic procedures (Lim et al., Evaluating the efficacy of EMLA topical anesthetic in sealant placement with rubber dam – Pediatr Dent 2004), intraligamentary and palatal mucosa injections (Meechan et al., A comparison of 2 topical anesthetics on the discomfort of

intraligamentary injections: a double-blind, split-mouth volunteer clinical trial – Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; Meechan., The use of EMLA for an intraoral soft-tissue biopsy in a needle phobic: a case report – Anesth Prog 2001). In addition, Munshi et al (Munshi et al., Use of EMLA: is it an injection free alternative? – J Clin Pediatr Dent. - 2001), suggested that some of the procedures could be carried out without dental needle, that is, with the topical application of EMLA only, especially in pedodontics.

In contrast, other authors call into question the superiority of EMLA when compared to other available anesthetics after concluding that 20% benzocaine was equivalent to EMLA in reducing the pain associated with anesthesia in palatal mucosa in children. Further, they reported that benzocaine has advantages over EMLA, such as higher volunteers preference and a more acceptable taste. Among disadvantages related to EMLA are included: bitter taste, high cost, and low viscosity, making it difficult to keep the cream at the desired site (Priemosch et al., Comparison of topical EMLA 5% oral adhesive to 20% benzocaine on pain experienced during palatal anesthetic infiltration in children – Pediatr Dent. 2001).

Ropivacaine is a local anesthetic belonging to the amide group and, like bupicavaine, has a long action time. As a topical anesthetic, it was noted that ropivacaine exhibits a good

efficacy and safety as compared to lidocaine, in cataract surgery, promoting analgesia with sufficient duration, in most cases without the need of supplementary anesthesia (Martini et al. Lidocaine versus ropivacaine for topical anaesthesia in cataract surgery – J Caract Refract Surg 2002).

The toxicity of ropivacaine on the oral mucosa has already been evaluated. Kawata et al (Kawata et al., Liquid chromatographic determination of plasma ropivacaine for assessing pharmacokinetics of the viscous preparation – Biol Pharm Bull 2005) performed a preliminary pharmacokinetic study in order to evaluate the safety of application of the anesthetic, in its viscous form, on the oral mucosa, for pain relief in carriers of oral cancer. The authors showed that the application of 5 mL of 0.5% ropivacaine solution on the oral mucosa, for 10 minutes, is safe, based on the plasma concentrations attained. However, its efficacy as a topical anesthetic was not evaluated.

The use of ropivacaine as topical anesthetic could be justified based upon its long anesthetic duration time, low potential of toxic effects on the cardiovascular system and the central nervous system (in comparison to bupivacaine), small plasma half-life, low potential for accumulation on tissues and high safety margin (Wang et al., Update on ropivacaine - Expert Opin Pharmacother 2001; Ramacciato et al., Recent advances in local anaesthesia – Dent Update 2005).

Although it is still unavailable for use in dentistry, ropivacaine has been studied for this purpose at concentrations ranging from 0.5 to 1% (Ramacciato et al., Recent advances in local anaesthesia – Dent Update 2005), being effective at 0.5% associated with epinephrine at 1:200,000 in maxillary infiltration anesthesia on the maxilla (Kennedy et al., Anesthetic efficacy of ropivacaine in maxillary anterior infiltration – Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001) and at 0.75% for inferior alveolar nerve block and for infiltration technique in the maxilla (Ernberg et al., Ropivacaine for dental anaesthesia: a dose-finding study – J Oral Maxillofac Surg 2002; Axelsson et al., The efficacy of ropivacaine as a dental local anaesthetic – Swed Dent J 2004).

Liposomes, which are being investigated and used as drug delivery vehicles, are also associated with anesthetics. Liposomes were discovered by Bangham, in 1963, and consist of spherical molecules measuring from 50 nm to 1000 nm in diameter and which result from the interaction of lipids suspended in an aqueous phase (Banerjee, Liposomes: applications in medicine - L Biomater Appl 2001; Grant, The Holy Grail: long-acting local anaesthetics and liposomes – Best Pratic Res Clin Anaesthesiol 2002). They can be formed by one or more lipid bilayers, respectively and so are called uni- or multilamellar vesicles.

Liposomes have a constitution similar to that of biological membranes, where the hydrophobic tails of the lipids are directed to the interior and the polar heads to the exterior, in contact to the aqueous phase (Ranade, Drug delivery systems. 1. Site-specific drug delivery using liposomes as carriers – J Clin Pharmacol 1989; Banerjee, Liposomes: applications in medicine - L Biomater Appl 2001), being able to carry both water-soluble and fat-soluble substances in their different phases (Grant, The Holy Grail: long-acting local anaesthetics and liposomes – Best Pratic Res Clin Anaesthesiol 2002).

The encapsulation of drugs in liposomes is oriented by the hydro- or lipophilicity thereof, since hydrophilic drugs have a tendency to remain in the central aqueous compartment and hydrophobic drugs in the interior of the lipid bilayer (Grant, The Holy Grail: long-acting local anaesthetics and liposomes – Best Pratic Res Clin Anaesthesiol 2002).

Local anesthetics are being encapsulated in liposomes (Fraceto et al, Spectroscopic evidence for a preferential location of lidocaine inside phospholipid bilayers – Biophys Chem 2002; de Paula et al., Molecular and physicochemical aspects of local anesthetic membrane interaction – Braz J. Med. Res., 1996; de Paula et al., Use of a novel method for determination of partition coefficient to compare the effect of local anesthetics on membrane structure – Biochim Biophys. Acta

1995), and some authors have already come to the conclusion that liposome-encapsulated bupivacaine showed reduced toxicity for the cardiovascular and central nervous systems when injected intravascularly in rabbits (Boogaerts et al., Plasma concentration of bupivacaine for the management of postsurgical pain: a first study – J Clin Anesth 1993, Grant et al.- J Pharmac Toxic. Methods 2000). The first study carried out in humans, the liposomal form of bupivacaine in the epidural technique, promoted higher analgesia duration with lower and constant plasma concentrations, when compared to the pure form of the local anesthetic (Boogaerts et al., Epidural administration of liposome-associated bupivacaine for management of postsurgical pain: a first study – J Clin. Anesth 1994).

The topical efficacy of local anesthetics has already been shown in dermatology. The similarity between vesicles and epidermal cells, in relation to its lipid composition, allows the anesthetic to penetrate through the epidermal barrier, reaching the deepest layers of dermis, promoting a slow release of the drug, protecting it against metabolization, and ensuring a higher anesthetic duration time (Friedman et al., Topical anesthetics update: EMLA and beyond – Dermatology Surg 2001).

In addition to this, liposomes are biocompatible, biodegradable, reducing the risk of: toxicity, immunogeneticity,

antigenicity, and histological lesions, especially due to the similarity between monomers which constitute liposomes (phosphatidylcholine and cholesterol) and those of biological membranes (Malinovsky et al., Neuroutoxicological assessment after intracisternal injection of liposomal bupivacaine in rabbits – Anesth. Analg 1997; Grant, The Holy Grail: long-acting local anaesthetics and liposomes – Best Pratic Res Clin Anaesthesiol 2002; Araújo et al., Formulações de anestésicos locais de liberação controlada: Aplicações Terapêuticas – Rev. Bras. Anestesiol. 2003).

The literature also reports that zwitterionic liposomes do not promote the lysis of erythrocytes and do not have a proagreggative effect on platelets; rather, it was shown that liposomal formulations of local anesthetics had a stronger effect on the inhibition of platelet aggregation induced by agents than when local anesthetics were used individually (Pinto et al, Influence of lipossomal-local anesthetics on platelet Aggregation in vitro – J. Lipos. 2004).

Liposomes have already been widely used as controlled release systems for various drugs, including antineoplasics, antibiotics, antifungals, and also local anesthetics for medical use (Bucalo et al., Comparison of skin anesthetic effect of liposomal lidocaine, non-liposomal lidocaine, and EMLA using 30-minute application time – Dematol. Surg 1998).

Many studies have showed the efficacy of liposome-encapsulated local anesthetics in topical anesthesia on skin (Singh et al., Topical liposomal system for localized and controlled drug delivery – J Dermatol Sci 1996; Bucalo et al., Comparison of skin anesthetic effect of liposomal lidocaine, non-liposomal lidocaine, and EMLA using 30-minute application time – Dematol. Surg 1998; Fisher et al., Topical anaesthesia of intact skin: liposome-encapsulated tetracaine vs EMLA – Br J Anesth 1998; Eichenfield et al., A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children - Pediatrics 2002; Taddio et al., Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial – Can Med. Assoc. J. 2005). Foldvari (Foldvari, In vitro cutaneous delivery and in vivo efficacy of tetracaine from liposomal and conventional vehicles – Pharm Res. 1994) has shown that the skin topical anesthesia provided by liposome-encapsulated tetracaine was deeper and had a lower onset time on the volunteers evaluated. Fisher et al. (Fisher et al., Topical anaesthesia of intact skin: liposome-encapsulated tetracaine vs EMLA – Br J Anesth 1998) have compared 5% liposome-encapsulated tetracaine with EMLA in their ability to produce topical anesthesia in intact skin, on 40 volunteers, and noticed a

more effective anesthesia and stronger preference of volunteers for the anesthesia provided by liposome-encapsulated tetracaine. It was also shown that the topical application of liposomal lidocaine for 30 minutes, without occlusive dressing, exhibits the same safety and efficacy in reducing pain caused by needle puncture as the euthetic mixture of lidocaine and prilocaine (EMLA), applied for 60 minutes, with occlusive dressing in 120 children (Eichenfield et al., A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with euthetic mixture of local anesthetics cream for pain reduction of venipuncture in children - Pediatrics 2002).

Friedman et al. (Friedman et al., Topical anesthetics update: EMLA and beyond – Dermatology Surg 2001) have compared the depth and duration of skin anesthesia produced by four topical anesthetics: EMLA, ELA-Max (4% lidocaine in liposomal vehicle), betacaine-LA (lidocaine + prilocaine + vasoconstrictor), and 4% tetracaine in gel. Tests were performed through laser stimulation at 10 locations in the forearm on 12 volunteers. Results showed the superiority of EMLA and liposomal lidocaine in the efficacy of anesthesia when compared to other preparations.

Recently, 4% lidocaine was evaluated in liposomal formulation as a skin topical anesthetic, previously to vein canulation in children. Results obtained after 30 minutes

application with occlusive dressing were: higher success rate, less pain, faster procedure time, and smaller amount of changes in dermis with respect to the placebo cream (Taddio et al., Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial – Can Med. Assoc. J. 2005).

The efficacy of the local anesthetic in liposomal form on oral mucosa was investigated only by Zed et al (Zed et al., Topical liposome encapsulated tetracaine versus benzocaine: a clinical investigation – J Dental Res.1996), which compared 5% liposome-encapsulated tetracaine to 20% benzocaine with respect to their ability to reduce pain related to puncture and infiltration of local anesthetic. They came to the conclusion that liposomal anesthetic was more effective in promoting relief of puncture pain.

The success of the topical treatment in mucosa depends on a suitable vehicle, which can have influence on the viability of the active component for absorption, penetration rate and time of permanence on the action site (Erjavec et al., In vivo study of liposomes as drug carriers to oral mucosa using EPR oximetry - Int J Pharm 2005).

It is estimated that oral mucosa has a permeability 4 to 4000 times higher than skin (Shojaei, Buccal mucosa as a route for systemic drug delivery: a review - J Pharm

Pharm Sci 1998). Accordingly, as anesthetic formulations exhibit a high success rate in topical anesthesia in the field of dermatology, it is expected that the success is still higher in oral mucosa, as the latter is more permeable than skin.

The anesthesia of small areas is frequently achieved with higher success by the use of an ointment or viscous gel (Yagiela et al, Farmacologia e Terapêutica para Dentistas - Guanabara Koogan 2000).

Local anesthetics comprise a great number of molecules having different chemical structures: amino-esters, amino-amides, amino-ketones, amides, alcohols, thio-esters. thio-amides, urea derivatives, polyethers, etc. (Gupta, Quantitative structure-activity relationship studies on local anesthetics - Chem. Rev 1991), which are able to block the conduction of the nervous stimulus. In the medical and dental practice, the most commonly used anesthetics are those from the amino-amide type (lidocaine, prilocaine, mepivacaine, and bupivacaine) and those from the amino-ester type (tetracaine). Although amino-esters are generally stronger than amino-amides (Covino et al., Local Anesthetics: mechanisms of action and clinical use, Grune and Stratton, New York 1976), the current trend is towards the employment of amino-amides, as they are less toxic and more resistant to hydrolysis when compared to amino-esters (Jong, Local anesthetics, 1st ed. – USA Mosby-Year Book 1994).

As amphiphilic molecules, local anesthetics have a great affinity for cellular membrane. In excitable membranes, they reduce the depolarization rate, inactivating sodium channels and, thus, preventing the inflow of ions required for depolarization of the membrane (Covino et al., Local Anesthetics: mechanisms of action and clinical use, Grune and Stratton, New York 1976). Fat-solubility is critical for the penetration of the local anesthetic on the nervous membrane, which is formed mostly by lipids. On the other hand, water solubility is critical for carrying the drug to the nervous fibers. For these reasons, the existence of a balance between these two characteristics becomes a factor of great importance for anesthetic activity (de Paula & Schreier, Molecular and physicochemical aspects of local anesthetic membrane interaction – Braz J. Med. Res.,1996; by Paula & Schreier, Use of a novel method for determination of partition coefficient to compare the effect of local anesthetics on membrane structure – Biochim Biophys. Acta 1995). The higher its water solubility, the faster will be the speed at which the anesthetic reaches the membrane and at which it will be removed from the action site, what reduces the duration of its effect. The higher is the fat-solubility of the anesthetic, the easier will be its penetration on the nervous membrane, which will reflect biologically on higher anesthetic power. The following table shows the properties of the main local anesthetics.

AL	pKa[b]	Water solubility of the neutral form (mM)[b]	Partition coefficient of neutral form	Potency[c]	Anesthesia time (h)[c]	Half-life (h)[c]
Procaine	9.2	16.3	84[b]	1	1	0.1
Mepivacaine	7.6	8.82	98[b]	2	1.5	1.5
Prilocaine	7.9	23.1	110[b]	3	1.5	1.5
Chlorprocaine	9.2	1.98	250[b]	4	0.75	0.1
Lidocaine	7.8	13.1	144[b]	4	1.5	1.5
Benzocaine	...	4.4	253[a]	n.d	n.d	n.d
Tetracaine	8.5	0.76	868[b]	16	8	2.5
Bupivacaine	8.1	0.58	798[b]	16	8	2.5
Etidocaine	7.7	0.16	1202[b]	16	8	3.0

n.d. = not determined; a: Pinto et al, 2000; b: by Paula & Schreier, 1995; c: Covino & Vassalo, 1976

The choice of topical formulations in gel form for carrying local anesthetics in liposomes was due to the increase on bioadhesion provided by these preparations. Among various drug controlled-release systems, transdermal systems show some advantages on the release control, as they extend the period of time during which the drug is in contact with the tissue where it was applied.

The percutaneous administration of bioadhesive gels enables ready application and easy removal. The use of products which enhance penetration, such as bile salts, surfactants, fatty acids, and its derivatives may be significant (Shin, et al., Preparations and evaluations of bioadhesive benzocaine gels for enhanced local anesthetic effects - Int. J. Pharm 2003).

By incorporating the local anesthetic in a viscous vehicle, such as a gel or ointment, they remain in contact with the area of application for a longer period, thus increasing the duration of the anesthetic action (Bennett et al - Anestesia local e Controle da Dor na Prática Dentária. Guanabara Koogan 1989). The combination of suitable components provides these formulations with excellent rheological characteristics, as it allows the formulation, upon application on the region of buccal mucosa (body temperature), not to show any significant decay on the viscosity curve. Other important factor that must be present in these formulations is the minimal hysteresis area on the rheological profile curves, which denotes that the same, upon undergoing shear stress, they quickly recover their tridimensional structure, which indicates high stability.

Rheological analysis of this kind, carried out in a commercial formulation largely used in dentistry, show high hysteresis and low viscosity at oral temperature, what is considered unfavorable for allowing these preparations to reach other locations within the oral cavity, causing some inconvenience to the patient, such as the anesthesia of regions that should not undergo the action of these products and even its accidental ingestion.

The present invention refers to pharmaceutical compositions of local anesthetic gels having stable viscosity when

subjected to a temperature in the range of 5°C to 50°C for topical application on buccal mucosa intended for use in dental procedures.

US5446063 discloses formulations and procedures for preparing an anesthetic composition for topical use, with a high concentration of the local anesthetic benzocaine in micronized form. Micronized benzocaine is dispersed or suspended in an emollient vehicle, wherein said vehicle may be in a lotion, ointment, or gel pharmaceutical form. In addition to not focusing on other local anesthetic mentioned in the present invention, except for benzocaine, the shown composition has the objective of improving the emollient power of the product in order to cause a pleasant contact with skin, which characteristic is not relevant to the oral cavity, where the maintenance of viscosity is the factor of major importance such as to provide bioadhesion and stability when in contact with body temperature. A bioadhesive local anesthetic gel allows easy application, easy removal, and longer contact time of the local anesthetic.

US4937078, in spite of comparing drug release systems with the presence of liposomes and without the presence of liposomes, is not directed to the gel pharmaceutical form, which is characterized by the relative viscosity that contributes, among other features, to the bioadhesion of the product. The time period during which other pharmaceutical forms, like lotions,

solutions, and unguents remain on the application site is reduced by temperature and motion factors, or the like, and besides being readily applicable, the gel has the advantage of being easily removable. Further, the rheological properties of the present invention are excellent for dental procedures, as they allow the formulation, upon application on the region of the oral mucosa, not to show any significant decay on the viscosity curve.

US663457 discloses compositions and methods for controlled drug release having a relatively low molecular weight through hydrogels, dispersing or dissolving such drugs in hydrophobic agents for giving a form to a mixture. The mixture is comprised of particles dispersed in hydrogel, for releasing water-soluble drugs in a controllable manner.

US4839175 discloses a formulation intended for ophthalmic use, comprising liposomes, which can be suspended in an aqueous means, containing a high viscosity polymer for further enhancing the holding of the active principle on the cornea. However, this document does not make any references to the product stability with respect to the temperature and time of the product when being used for controlled release of the active principle.

Although in the documents formulations having the gel pharmaceutical form with considerable viscosity are shown, none of the formulations has the characteristic of viscosity

stability with respect to time and temperature. These characteristics are critical in gels intended for use in dentistry.

For these reasons, there has been a growing interest in the development of topical formulations for local anesthetics which combine increased anesthetic power without increasing systemic toxicity, maintaining optimal bioadhesion and viscosity characteristics for body temperature. The present invention meets this need, as it relates to the association of local anesthetics with an ideal vehicle for topical application, promoting extended release of the anesthetic, which remains for a longer time and at a higher concentration on the action site, consequently increasing its efficacy.

Objects of the invention

The subject invention aims to solve the problems encountered in the local anesthetic formulations for use in dentistry concerning the rheological instability during storage and application and, accordingly, the consequences resulting from this rheological instability.

Summary of the invention

The present invention relates to a pharmaceutical composition which comprises a pharmaceutically

effective amount of at least one anesthetic and at least one gelling agent, said composition having a minimum viscosity of 30 Pa.s, when subjected to a temperature ranging from 5°C to 50°C.

This invention also refers to the use of a pharmaceutically effective amount of anesthetic and gelling agent for the preparation of a pharmaceutical composition having a minimum viscosity of 30 Pa.s.

The present invention further refers to a process for obtaining said pharmaceutical composition, comprising the following steps:

i. Micronizing the local anesthetic(s);

ii. Adding a levigating agent;

iii. Adding a gelling agent;

iv. Adding a preservative and a wetting agent;

v. pH adjusting, through the addition of an alkalizing agent.

In addition, this invention still refers to a product comprising a pharmaceutically effective amount of at least one anesthetic and at least one gelling agent, said product having a minimum viscosity of 30 Pa.s, when subjected to a temperature ranging from 5°C to 50°C.

This invention also refers to a method of pain treatment which comprises administering a pharmaceutical composition to a person who is in need of this treatment, which

comprises a pharmaceutically effective amount of at least one anesthetic and at least one gelling agent, said composition having a minimum viscosity of 30 Pa.s, when subjected to a temperature ranging from 5°C to 50°C.

Brief description of the drawings

Figure 1 shows a process for the gelling of the carboxyvinyl polymer resin through the addition of triethanolamine;

Figures 2A and 2B show comparative graphs for the rheological profile of 10% (A) and 15% (B) benzocaine gel at temperatures of 23°C and 36°C.

Figures 3A and 3B show comparative graphs for the rheological profile of 10% (A) 15% (B) liposomal benzocaine gel and at temperatures of 23°C and 36°C.

Figure 4 shows the rheological profile of commercial benzocaine gel (20%) at temperatures of 23°C and 36°C. The presence of hysteresis is denoted by the arrows.

Figures 5A and 5B show comparative graphs for the rheological profile of benzocaine gel at 23°C (A) and 36°C (B), at concentrations of 10% and 15%.

Figures 6A and 6B show comparative graphs for the Rheological profile of liposomal benzocaine gels, at 23°C (A) and 36°C (B), at concentrations of 10% and 15%.

Figures 7A, 7B, 9C, and 9D show comparative

graphs between viscosity of liposomal (B) and non-liposomal (A) 10% benzocaine gels and liposomal (D) and non-liposomal (C) 15% benzocaine, at temperatures of 23°C and 36°C.

Figure 8 shows a viscosity graph of the commercial product (20% benzocaine gel) at temperatures of 23°C and 36°C.

Figures 9A, 9B, 9C, and 9D show comparative graphs between viscosity of liposomal and non-liposomal 10% benzocaine gels at 23°C (A) and 36°C (B) and liposomal and non-liposomal 15% benzocaine at 23°C (C) and 36°C (D).

Figures 10A, 10B, 10C, 10D, E, F, G, H, I, and J show comparative graphs of the comparative Rheological profile between two temporal analyses (May and October/2005), carried out at temperatures of 23°C (left) and 36°C (right) for 10% benzocaine (A, B), liposomal 10% benzocaine (C, D), 15% benzocaine (E, F), liposomal 15% benzocaine (G, H), and 20% benzocaine (I, J) formulations.

Figures 11E, 11F, 11G, 11H, 11I, and 11J show comparative graphs of the comparative Rheological profile between two temporal analyses (May and October/2005), carried out at temperatures of 23°C (left) and 36°C (right) for 15% benzocaine (E, F), liposomal 15% benzocaine (G, H), and 20% benzocaine (I, J) formulations.

Figures 12A, 12B, 12C, 12D, 12E, and 12F

show comparative graphs of the comparative Rheological profile, at 4 temperatures (8, 23, 36 and 50°C) between liposomal (A) and non-liposomal (A) 10% benzocaine, liposomal (D) and non-liposomal (C) 15% benzocaine formulations, and between 20% benzocaine (F) and the commercial preparation of 20% benzocaine (E).

Figures 13A, 13B, 13C, 13D, 13E, and 13F show comparative viscosity graphs, at 4 temperatures (8, 23, 36 and 50°C) between liposomal (B) and non-liposomal (A) 10% benzocaine, liposomal (D) and non-liposomal (C) 15% benzocaine formulations, and between 20% benzocaine (F) and the commercial preparation of 20% benzocaine (E).

Figures 14A and 14B show comparative graphs for the rheological profile of 2% ropivacaine gel, with liposomes (B) and without liposomes (A), at the temperature of 36°C.

Figure 15 shows the viscosity of 2% Ropivacaine, with and without liposomes, at 36°C.

Figure 16 shows the cumulative benzocaine release (%) in solution, in unilamellar liposome formulations and in the carboxyvinyl polymer matrix, also in solution. Data represented as means ± SD (n=3).

Figure 17 shows median values in the Visual Analog Scale of pain, obtained with liposome-encapsulated 1% ropivacaine gel and 1% Ropivacaine gel. * (p= 0.0128).

Figure 18 shows median values in the Visual Analog Scale of pain, obtained with liposome-encapsulated 10% benzocaine gel and 10% benzocaine gel ($p>0.05$).

Figure 19 shows median values in the Visual Analog Scale of pain, obtained with 20% benzocaine gel, EMLA, and liposome-encapsulated 1% Ropivacaine gels, and liposome-encapsulated 10% benzocaine.

Figure 20 shows median values of anesthesia duration in soft tissues for liposome-encapsulated 1% ropivacaine gel and 1% ropivacaine gel ($p=0.0009$).

Figure 21 shows median values of anesthesia duration in soft tissues for liposome-encapsulated 10% benzocaine gel and 10% benzocaine gel ($p=0.0198$).

Figure 22 shows median values of anesthesia duration in soft tissues for liposome-encapsulated 10% benzocaine gel, liposome-encapsulated 1% ropivacaine gel, EMLA, and commercial 20% benzocaine gel.

Detailed description of the invention

The present invention discloses a pharmaceutical composition for local anesthetic gel which allows improved penetration of the anesthetic by maintaining the drug for a longer time and at a higher concentration on the action site, which increases the duration of anesthesia while reducing its toxicity, in addition to restricting the action of the drug to the

application site. The maintenance of the drug for a longer time and at higher concentration on the action site is made possible as this anesthetic gel shows a smaller variation in its viscosity when subjected to a temperature increase resulting from the contact with the buccal mucosa.

The pharmaceutical composition of the present invention comprises a pharmaceutically effective amount of at least one anesthetic and at least one gelling agent, said composition having a minimum viscosity of 30 Pa.s, when subjected to a temperature ranging from 5°C to 50°C. The anesthetic used in the composition is micron zed, wherein micronization can be performed by means of an organic solvent, mechanical grinding, or other suitable methods. Among organic solvents that can be used are absolute alcohol, acetone, chloroform, and other proper solvents.

The local anesthetic used for the subjected composition is selected from the group consisting of benzocaine, tetracaine, procaine, articaine, lidocaine, ropivacaine, bupivacaine, prilocaine, or any mixture thereof, preferably benzocaine or ropivocaine or a mixture between lidocaine and prilocaine is used. The local anesthetic is at a concentration range of 0.1% to 20% by weight. More specifically, anesthetics which are considered long-acting, such as bupivacaine, lidocaine, prilocaine, mepivacaine, are present in a range from 0.1% to 10%

by weight, and benzocaine is present in a range from 5% to 20% by weight.

In the pharmaceutical composition of the present invention, the local anesthetic may be partiality encapsulated in liposomes. Liposomes are obtained from a mixture of egg lecithin, vitamin E, and cholesterol, but can also be obtained from other sources.

The gelling agent used in the present invention comprises a carboxyvinyl polymer which is used at a concentration of 0.5% to 2% by weight. Preferably, the gelling agent is used at a concentration of 1% to 2% by weight.

The gelling agent, when present in the composition, produces a minimum viscosity of 30 Pa.s and maintains this characteristic in a temperature range from 5°C to 50°C.

The gelling agent, when present in the composition, attains rheological properties as shown in figure 1.

The pharmaceutical composition of the present invention comprises a levigating agent, selected from white mineral oil, glycerine, propylene glycol, polyethylene glycol 400, castor oil, cotton oil, polysorbate 80. Preferably, propylene glycol is used. When used, propylene glycol makes up 5 to 15%, by weight, of the present composition.

The composition of the present invention also comprises a wetting agent, which is selected from the group consisting of glycerine, sorbitol, propylene glycol, polyethylene glycol 400, or any mixture thereof. Preferably, glycerine is used as the wetting agent. When used, glycerine makes up 2% to 5%, by weight, of the present composition.

The composition of the present invention also comprises an amount of alkalizing agent suitable for the pH adjustment of the composition in the range of 4.5 to 11, preferably for the pH adjustment to 7.

The alkalizing agent used comprises an inorganic base and/or low molecular weight amine. The inorganic base preferably used is sodium hydroxide and the low molecular weight amine preferably used is triethanolamine (TEA).

The composition of the present invention also comprises an antimicrobial preservative, wherein methylparaben is preferably used. When used, methylparaben makes up 2% by weight of the composition.

The composition of the present invention also comprises a sweetener selected from saccharin, stevia, and aspartame.

The subject invention also refers to the use of a pharmaceutically effective amount of anesthetic and gelling agent

for the preparation of a pharmaceutical composition having a minimum viscosity of 30 Pa.s.

The pharmaceutical composition described in the present invention is used for dental and/or dermatological treatment, as well as other treatments in which the presence of a local anesthetic is necessary.

The composition to which this invention refers shows, in addition to rheological characteristics typical of gels, a relatively stable temperature when in contact with the buccal mucosa and comprises the combination of the following components:

- ✓ a local anesthetic;
- ✓ a pharmaceutically acceptable wetting agent at a minimum concentration of 2%; by weight
- ✓ propylene glycol at a concentration of 5% to 15%; by weight
- ✓ a carboxyvinyl propylene at a concentration of 0.5% to 2%; by weight
- ✓ an alkalizing agent, at a concentration adequate for obtaining a pH of 4.5 to 11.
- ✓ a pharmaceutically acceptable antimicrobial preservative at a concentration of 2%.

The subject invention also refers to a process for obtaining said pharmaceutical composition comprising the steps of:

vi. Micronizing the local anesthetic(s);

vii. Adding a levigating agent;

viii. Adding a gelling agent;

ix. Adding a preservative and a wetting agent;

x. pH adjusting, through the addition of an alkalizing agent.

Firstly, micronization of the particles of the anesthetic is carried out by contacting the same with the organic solvent in a porcelain mortar, this procedure is called manual grinding and typically used in small-scale production. Among organic solvents employed are acetone, ethanol, chloroform, or other pharmaceutically acceptable solvents. The organic solvent should be used in a minimal amount, yet able to wet the active principle and break the stiffness of its particles, dissolving it and automatically making its grinding easier. The main requirement that should be noted is the full evaporation of the organic solvent before any other step of the pharmacotechnical procedure. Other methods, such as grinders and atomizers comprising a mechanical grinding typically used in large-scale production may be used for reducing particle size. After micronizing the anesthetic, the

organic solvent is removed through evaporation. On a small scale, this removal of the organic solvent can be carried out in a fume hood for a period of 8 hours. After removing the organic solvent, the levigating agent propylene glycol is added. The levigating agent further reduces the particle size of the anesthetic, forming a paste of solid material, avoiding roughness in the formulation, and also acting as a solvent and wetting agent. Among levigating agents that may be used are white mineral oil, glycerine, propylene glycol, polyethylene glycol 400, castor oil, cotton oil, polysorbate 80, as well as other suitable levigating agents. Preferably, propylene glycol is used. Following levigation, the drug may be optionally put in contact with a liposomal solution, remaining in contact therewith for a minimum period of 2 h. The liposomal solution may be obtained through a mixture of egg lecithin, vitamin E, and cholesterol, or from other sources, and shows a large unilamellar liposome size of about 400 nm (LUV 400 nm). It is important to point out that, like in every liposomal system, the active principle, in this case, the anesthetic, is partially encapsulated in liposomes. After contact with a liposomal solution (when this option is employed) or after levigation with propylene glycol (when liposomal solution is not used), a carboxyvinyl polymer is added, waiting until intumescence under gentle stirring. Carboxyvinyl polymers that can be used include, but are not limited to, Carbopol 934 or Carbopol 840 or Carbopol

2020 or Carbopol Ultrez. Preferably, the carboxyvinyl polymer Carbopol 934 is used.

Next, an antimicrobial preservative, a wetting agent, and other components, such as water and, alternatively, sweeteners, are added. As an antimicrobial preservative, any pharmaceutically acceptable antimicrobial preservative can be used, preferably methylparaben at a concentration of 2%. Among wetting agents, any pharmaceutically acceptable wetting agent may be used, preferably sorbitol, propylene glycol, glycerine, polyethylene glycol 400 (PEG 400), or any mixture thereof, amounting to a minimum concentration of 2% in the final solution. The sweetener, when used, is selected from saccharine, stevia, or aspartame. The final pH of the process and, consequently, the gelling of the obtained mixture are controlled by adding, in the end of the process, an alkalizing agent in a sufficient amount to obtain a pH of 4.5 to 11. Preferably, the final pH of the formed gel is 7.0.The alkalizing agent used comprises an inorganic base or low molecular weight amine. Preferably, as an inorganic base, sodium hydroxide is used, and as a low molecular weight amine, thriethanolamine is used.

The carboxyvinyl resin or polymer, when dispersed in water, is hydrated and forms an aqueous dispersion (resin/water) having a pH value in the range of 2.8 to 3.2. In this pre-dissolved state, the carboxyvinyl macromolecule is extremely

folded and its thickening ability is restricted. In order to provide thickening, neutralization with inorganic bases is required, wherein sodium hydroxide and low molecular weight amines are preferably used, such as triethanolamine (TEA).

By adding the inorganic base or low molecular weight amine, the carboxyvinyl polymer stretches itself due to the neutralization of the carboxyl groups present in the polymer. A schematic view of this stretching is shown in Figure 1.

The maximum viscosity and transparency in the carboxyvinyl polymer gel is attained with pH 7, but an acceptable viscosity and transparency starts from pH 4.5 to 5 and extends up to pH 11.

The product obtained in the present invention comprises a pharmaceutically effective amount of at least one anesthetic and at least one gelling agent, said composition having a minimum viscosity of 30 Pa.s, when subjected to a temperature ranging from 5°C to 50°C.

In the following paragraphs some exemplary compositions of the anesthetic gel of the invention are shown. The examples shown herein should be construed as one possible way of embodying the invention and, therefore, are not intended to restrain the scope of protection thereof.

✓ Example 1:

Carbopol (carboxyvinyl polymer) 0.5% - 2%

Propylene glycol 5% - 15%

Glycerine 2% - 8%

Nipagin (methylparaben) 0.2%

Liposomal suspension 4 mM (final concentration).

Thriethanolamine qs to pH = 7.0

Water qs to 30 g of the formulation.

✓ Example 2:

Carbopol 0.5% - 2%

Propylene glycol 5% - 15%

Glycerine 6% - 8%

PEG 400 2% - 8%

Nipagin 0.2%

Liposomal suspension 4 mM (final concentration).

Thriethanolamine qs to pH = 7.0

Water qs to 30 g of the formulation.

✓ Example 3:

Carbopol 1%

Propylene glycol 5% - 15%

Glycerine 4% - 8%

Sorbitol 4% - 15%

Nipagin 0.2%

Liposomal suspension 4 mM (final concentration).

Thriethanolamine qs to pH = 7.0

Water qs to 30 g of the formulation.

✓ Example 4:

Carbopol 0.5% - 2%

Propylene glycol 5% - 15%

Glycerine 4% - 8%

PEG 400 2% - 8%

Sorbitol 2% - 15%

Nipagin 0.2%

Liposomal suspension 4 mM (final concentration).

Thriethanolamine qs to pH = 7.0

Water qs to 30 g of the formulation.

✓ Example 5:

Carbopol (carboxyvinyl polymer) 0.5% - 2%

Propylene glycol 5% - 15%

Glycerine 2% - 8%

Nipagin (methylparaben) 0.2%

Thriethanolamine qs to pH = 7.0

Water qs to 30 g of the formulation.

Rheological study

The formulations show characteristics typical of

gels, with a desirable viscosity for products for application in buccal mucosa and low hysteresis when compared to the commercial formulation, ensuring the stability thereof.

In order to characterize the obtained product, analyses of its rheological profile were carried out. The rheological profile graph (shear rate (s^{-1}) x shear stress (Pa)) is composed of two curves, one being the increase on the strain rate and the other being the decrease of this parameter. When there is a distancing between these two curves, we are in the presence of a phenomenon called hysteresis, according to which that the analyzed product, upon experiencing a given stress, exhibited strain in its tridimensional structure, which strain was not recovered when stress was released. This denotes low stability and reduced shelf-time of the analyzed formulation.

For this study, the local anesthetic chosen for incorporation on the prepared base was benzocaine, for being widely-used in dentistry, wherein the reference commercial product, which was chosen for comparative analysis, has as an active principle this anesthetic. At buccal temperature (36°C ± 1°C), the local anesthetic ropivacaine was also analyzed in order to ascertain whether the presence of another active principle would otherwise change the rheological results.

The formulations described in the present invention were analyzed as to the rheological profile thereof and

compared with the rheological profile of commercial formulations.

By analyzing the behavior of the rheological profile curves from non-liposomal benzocaine gels at concentrations of 10% (Figure 2A) or 15% (Figure 2B), but at different temperatures (23°C and 36°C), it can be noted that the rheological curve associated with the temperature of 36°C has a lower slope, what shows a less evident viscosity when compared to the higher slope curve associated with the temperature of 23°C. The same was observed for liposomal benzocaine gels at equal concentrations, but at different temperatures (Figure 3A and Figure 3B). The above described fact was also seen in the commercial product analyzed (Figure 4). Another important information obtained from the analysis of the rheological profile curves is the presence or absence of hysteresis (distancing between the upward curve and the downward curve which describe the rheological behavior). Focusing on the pharmaceutical formulations analyzed in this study, the presence of hysteresis characterizes a negative factor, since it means that the analyzed product, upon undergoing stress, is not capable of returning to its initial form when this stress stops being applied on it. This implicates in low stability and, as a result, reduced shelf-time for these formulations. The higher the hysteresis, the lesser is the stability of the analyzed product. This can be seen on the

rheological profile graph of the commercial formulation, shown in Figure 4, at two temperatures (23°C and 36°C); hysteresis is evidenced by the double-way arrows.

The analysis of the behavior of the rheological profile curves of non-liposomal benzocaine gels at different concentrations, but at equal temperatures (Figure 5A and Figure 5B) showed that the rheological curve associated with 15% benzocaine has a higher slope, what indicates a more evident viscosity when compared to the lower slope curve associated with 10% benzocaine. By analyzing the rheological behavior of liposomal benzocaine gels (Figure 6A and Figure 6B), we noticed that the higher slope occurred on the rheological curve associated with benzocaine at a concentration of 10%, showing a more evident viscosity when compared to liposomal benzocaine gel at 15%. Data from calculation of hysteresis area at 23°C, in Pas.s and at 36°C, in Pas.s., are shown in the following tables:

Gel (23°C)	**A** upward curve	**A** downward curve	**A** absolute hysteresis	**A** relative hysteresis
10% BZC	90522.02	- 99674.79	9152.77	7.316
15% BZC	101981.88	- 106759.08	4777.20	3.517
COMMERCIAL 20% BZC	73408.09	- 253631.40	**180223.31**	**100.458**
LIPOSOMAL 10% BZC	124008.20	- 136075.85	12067.65	6.214
LIPOSOMAL 15% BZC	173453.81	- 184424.96	10971.15	5.455

Gel (36°C)	A upward curve	A downward curve	A absolute hysteresis	A relative hysteresis
10% BZC	81400.06	- 88361.68	6961.62	5.991
15% BZC	92002.33	- 90905.73	- 1096.60	- 0.904
COMMERCIAL 20% BZC	54040.49	- 153653.35	**99612.86**	**93.974**
LIPOSOMAL 10% BZC	138346.52	- 134303.98	- 4042.54	- 2.144
LIPOSOMAL 15% BZC	145675.71	- 136366.94	- 9308.77	- 5.517

Apart from rheological profile curves, the behavior of these gels can be also shown in viscosity graphs (Figures 7 to 9). By analyzing these graphs, we observed that in liposomal and non-liposomal benzocaine gels, when compared at equal concentrations and different temperatures, viscosity is slightly evident on the curve associated with the temperature of 23°C (Figure 7). However, in the commercial product (non-liposomal 20% benzocaine gel), the difference in viscosity was much higher, showing a relatively abrupt consistency change when there is a variance in temperature (Figure 8).

Viscosity graphs of the gels at equal temperatures and concentrations, but in the absence or presence of liposomes, were also built in order to ascertain whether the presence of these vesicles would cause any modification on the subject parameter. After analyzing these graphs, we have found that viscosity curves associated with liposomal formulations showed a higher height, what demonstrates they have a more

evident viscosity when compared to non-liposomal formulations, at all times (Figure 9).

The analyses previously shown were repeated after five months in order to ascertain the stability of these formulations in the course of time. For this new analysis, two new temperature values were added, one of which is 8°C (reproducing the temperature of a refrigerator) and the other 50°C (reproducing the eventual predisposition of these formulations to the non recommended temperature). The found results show that the gels corresponding to the new formulations continued not showing significant hysteresis when compared to those present in the commercial formulation, even at the new temperature values introduced in this study, which characterizes the stability of these new products both in liposomal and non-liposomal formulations. Comparative graphs between the rheological profile found at the first analysis and that subsequently performed at the temperatures of 23°C and 36°C were built, evidencing what was described previously (Figure 10).

Tables with different temperatures, from 23°C to 30°C, corresponding to hysteresis variation between the two analyses, one on May and the other on October, were built for better viewing this parameter, denoting high values on the commercial formulation, as follows:

Gel (23°C)	**A** absolute hysteresis **may2005**	**A** absolute hysteresis **oct.2005**	**A** relative hysteresis **may2005**	**A** relative hysteresis **oct.2005**
10% BZC	9152.77	7480.0113	7.316	4.973
15% BZC	4777.20	1754.2285	3.517	1.474
COMMERCIAL 20% BZC	180223.31	150288.3066	100.458	95.081
LIPOSOMAL 10% BZC	12067.65	83.713	6.214	0.0393
LIPOSOMAL 15% BZC	10971.15	5714.7645	5.455	3.099

Gel (36°C)	**A** absolute hysteresis **may2005**	**A** absolute hysteresis **oct.2005**	**A** relative hysteresis **may2005**	**A** relative hysteresis **oct.2005**
10% BZC	6961.62	-6777.8456	5.991	-4.940
15% BZC	-1096.60	3645.3665	-0.904	2.852
COMMERCIAL 20% BZC	99612.86	67521.2643	93.974	85.534
LIPOSOMAL 10% BZC	-4042.54	4244.8105	-2.144	2.150
LIPOSOMAL 15% BZC	-9308.77	-2201.0635	-5.517	1.3117

According to the time period described (May and October) and the difference of the analyzed temperatures, a comparison of the gel viscosity variation was carried out, wherein these data can be better seen in the following tables or in figure 11.

Gel	A_{curve} **May2005**	A_{curve} **oct.2005**	**Δ viscosidade**
10% BZC	2450.88904	2700.64566	- 249.75662
15%BZC	2618.72333	2196.49452	422.22881
COMMERCIAL	4299.17505	3681.8833	617.29175

20% BZC			
LIPOSOMAL 10% BZC	3960.16785	3840.20965	119.9582
LIPOSOMAL 15% BZC	3490.33935	3105.58065	384.7587

Gel	**A_{curve} May2005**	**A_{curve} oct.2005**	**Δ viscosidade**
10% BZC	2317.43608	2429.69586	-112.25978
15% BZC	2316.32888	2422.10932	-105.78044
COMMERCIAL 20% BZC	2357.98989	1634.02974	723.96015
LIPOSOMAL 10% BZC	3684.2565	3604.4051	79.8514
LIPOSOMAL 15% BZC	3003.2351	2921.53648	81.69862

As two new temperature values were added, comparative rheological profile graphs between the four temperatures were built (Figures 12 and 13), showing that in the gels described in the invention hysteresis remained at a minimum even at extreme temperatures, such as 8°C and 50°C, maintaining its initial three-dimensional structure; however, in the commercial formulation, the same remained evident. Another important modification on this analysis (Figures 12 and 13) was the introduction of a 20% benzocaine gel prepared on the same base as the others already analyzed; this was taken into account in checking whether this anesthetic concentration would change our results, since the commercial product, which contains anesthetic at this concentration, exhibits a significant hysteresis and a

consequent reduction on parameters like viscosity and stability. Results showed that the gel prepared with this anesthetic concentration remained with a low hysteresis and optimum viscosity, which denotes that the prepared base is responsible for providing an optimum support for these formulations to withstand both temperature and anesthetic variations (Figure 12).

Comparative viscosity graphs at the same temperatures (Figure 13) were also built, showing that the gels associated with the new formulations had reduced decay in this parameter even at a high temperature (50°), which is an important data since they are able do withstand high temperatures without significant changes with reference to the physical characteristics thereof. This previously mentioned fact was not observed in the commercial formulation, which liquefied at this temperature.

Analyses performed with the subject pharmaceutical base using the anesthetic ropivacaine in order to check whether the presence of another active principle would otherwise change rheological results, showed that the presence of hysteresis remained reduced on the liposomal formulation, as well on the non-liposomal formulation (Figure 14), and that an optimum viscosity level remained at the temperature of interest – buccal temperature: 36°C ± 1°C (Figure 15), as shown below in the comparative hysteresis calculation of ropivacaine gels with the commercial product and benzocaine formulations at a temperature

of 36°C.

Gel (36°C)	$A_{absolute\ hysteresis}$	$A_{relative\ hysteresis}$
2% Ropi	-11151.7915	-8.116
Liposomal 2% Ropi	-14058.212	-11.504
10% Benzocaine	-6777.8456	-4.940
15% Benzocaine	3645.3665	2.852
Commercial product	**67521.2643**	**85.534**
Liposomal 10% Benzocaine	4244.8105	2.150
Liposomal 15% Benzocaíne	-2201.0635	1.3117

The release of free and encapsulated drugs was observed using a system described by Paavola et al. (1995), with the use of a cellulose membrane (with MWCO pores having 12000 to 14000 Da). Generally, tests showed a decrease on the release of encapsulated anesthetics with respect to free drugs, indicating that the addition of a carrier changed the penetration of drugs through the membrane; This slow release rate of the liposomal formulation was very near to the formulation having the anesthetic in contact only with the matrix from the gel still in solution, which showed that this matrix act as an extended release system. Controlled release is based on the chemical structure of the gelling agent, which holds the anesthetic in a folded structure, as shows Figure 16 for the anesthetic benzocaine.

In addition to the *in vitro* test described above, thirty volunteers were subjected to topical anesthesia with six

anesthetics, in six sessions (treatments) randomly chosen. Treatments were carried out with 60 mg of each topical anesthetic: 1% Ropivacaine gel, liposome-encapsulated 1% Ropivacaine gel, 10% benzocaine gel, liposome-encapsulated 10% benzocaine gel, EMLA cream (EMLA®, AstraZeneca, Cotia, Brazil), and 20% benzocaine gel (Benzotop®, DFL Ind Com Ltda, Rio de Janeiro, Brazil). Each treatment was applied to the buccal fold of the upper-right canine during two minutes; the interval between treatments was of one week. The following were evaluated: duration of anesthesia in soft tissue by means of physical stimulus and efficacy of anesthetics as to pain reduction during needle puncture, during the simulation of an anesthesia with the infiltration technique, by means of the visual analog scale (VAS) of pain; on this scale, the higher the value, the higher is the pain sensitivity (Malamed, 2000).

Liposome-encapsulated 1% Ropivacaine gel was statistically more effective in reducing puncture pain, showing lower values on the Visual Analog Scale, as compared to 1% Ropivacaine gel ($p= 0.0128$). Figure 17 shows a comparison between median values from the Visual Analog Scale for liposome-encapsulated 1% Ropivacaine gel and 1% Ropivacaine gel.

Liposome-encapsulated 10% benzocaine gel was not statistically different from 10% benzocaine gel (p

=0.6592). Figure 18 shows a comparison between median values for the Visual Analog Scale for liposome-encapsulated 10% benzocaine gel and 10% benzocaine gel.

In comparison with commercial formulations currently available on the market, liposome-encapsulated 1% Ropivacaine gel was statistically superior in reducing puncture pain with respect to 20% benzocaine gel (p =0.0187). However, liposome-encapsulated 1% ropivacaine was not statistically superior to the other anesthetics evaluated (p>0.05). Thus, liposome-encapsulated 10% benzocaine was equivalent to all evaluated anesthetics and 1% ropivacaine was superior only to the commercial form of 20% benzocaine. Figure 19 shows median values for the Visual Analog Scale for 20% benzocaine gel, EMLA, and for liposome-encapsulated 1% Ropivacaine gels and liposome-encapsulated 10% benzocaine.

Liposome-encapsulated 10% benzocaine gel showed efficacy in reducing puncture pain similar to EMLA and 20% benzocaine, and liposome encapsulated 1% Ropivacaine gel was equivalent to EMLA and superior to 20% benzocaine as to its ability to reduce puncture pain. With respect to the duration of anesthesia in soft tissue, liposome-encapsulated 1% ropivacaine promoted a longer anesthesia duration in soft tissues as compared to non-encapsulated 1% ropivacaine (p=0.0009). Figure 20 shows the comparison between median values with respect to the

duration of anesthesia in soft tissues for liposome-encapsulated 1% Ropivacaine gel and 1% Ropivacaine gel.

Liposome-encapsulated 10% benzocaine promoted a longer duration of anesthesia in soft tissue as compared to non-encapsulated 10% benzocaine ($p=0.0198$). Figure 21 shows the comparison between median values with respect to the duration of anesthesia in soft tissues for liposome-encapsulated 10% benzocaine gel and 10% benzocaine gel.

Liposome-encapsulated 1% Ropivacaine gel showed longer anesthesia duration in soft tissues in comparison to the commercial form of 20% benzocaine gel ($p<0.05$), but did not show any statistical difference with respect to EMLA or liposome-encapsulated 10% benzocaine. Liposome-encapsulated 10% benzocaine gel did not show statistical differences with respect to the other anesthetics evaluated: liposome-encapsulated 1% ropivacaine, EMLA, or commercial 20% benzocaine gel ($p>0.05$). EMLA showed longer anesthesia duration in soft tissues with respect to liposome-encapsulated 10% benzocaine and commercial 20% benzocaine gel ($p<0.005$). Figure 22 shows the comparison of the median values with respect to the duration of anesthesia in soft tissues for liposome-encapsulated 10% benzocaine gel, liposome-encapsulated 1% Ropivacaine gel, EMLA, and commercial 20% benzocaine gel.

Claims

1. A pharmaceutical composition, characterized in that it comprises a pharmaceutically effective amount of at least one anesthetic and at least one gelling agent, said composition having a minimum viscosity of 30 Pa.s, when subjected to a temperature ranging from 5°C to 50°C.

2. Pharmaceutical composition, according to claim 1, characterized in that the local anesthetic is selected from: benzocaine, tetracaine, procaine, lidocaine, ropivacaine, bupivacaine, prilocaine, articaine, or any mixture thereof.

3. Pharmaceutical composition, according to any one of claims 1 to 2, characterized in that the local anesthetic is benzocaine.

4. Pharmaceutical composition, according to any one of claims 1 to 2, characterized in that the local anesthetic is ropivacaine.

5. Pharmaceutical composition, according to any one of claims 1 to 2, characterized in that the local anesthetic is a mixture of lidocaine and prilocaine.

6. Pharmaceutical composition, according to any one of claims 1 to 5, characterized in that the local anesthetic is at a concentration range of 0.1% to 20% by weight.

7. Pharmaceutical composition, according to any one of claims 1 to 6, characterized in that the local anesthetic is micronized.

8. Pharmaceutical composition, according to claim 7, characterized in that the micronized local anesthetic is obtained with the participation of an organic solvent.

9. Pharmaceutical composition, according to claim 8, characterized in that the organic solvent is selected from: absolute alcohol, acetone, chloroform.

10. Pharmaceutical composition, according to claim 7, characterized in that the micronized local anesthetic is obtained by means of mechanical grinding.

11. Pharmaceutical composition, according to any one of claims 1 to 10, characterized in that the local anesthetic is partially encapsulated in liposomes.

12. Pharmaceutical composition, according to claim 11, characterized in that the liposomes are obtained from a mixture of egg lecithin, vitamin E, and cholesterol.

13. Pharmaceutical composition, according to claim 1, characterized in that the gelling agent produces a minimum viscosity of 30 Pa.s and maintains this characteristic in a temperature range of 5°C to 50°C.

14. Pharmaceutical composition, according to claim 13, characterized in that the gelling agent comprises a carboxyvinyl polymer.

15. Pharmaceutical composition, according to claim 14, characterized in that the carboxyvinyl polymer is at a concentration range of 0.5% to 2.0% by weight.

16. Pharmaceutical composition, according to claim 14, characterized in that the carboxyvinyl polymer is at a concentration range of 1% to 2% by weight.

17. Pharmaceutical composition, according to claim 1, characterized in that said composition comprises a levigating agent.

18. Pharmaceutical composition, according to claim 17, characterized in that the levigating agent is selected from: white mineral oil, glycerine, propylene glycol, polyethylene glycol 400, castor oil, cotton oil, polysorbate 80.

19. Pharmaceutical composition, according to any one of claims 17 to 18, characterized in that the levigating agent utilized is propylene glycol.

20. Pharmaceutical composition, according to any one of claims 18 to 19, characterized in that the concentration of propylene glycol in the composition is of 5% to 15% by weight.

21. Pharmaceutical composition, according to claim 1, characterized in that said composition comprises a wetting agent.

22. Pharmaceutical composition, according to claim 21, characterized in that the wetting agent is selected from: glycerine, sorbitol, propylene glycol, polyethylene glycol 400, or any mixture thereof.

23. Pharmaceutical composition, according to any one of claims 21 to 22, characterized in that the wetting agent utilized is glycerine.

24. Pharmaceutical composition, according to any one of claims 22 to 23, characterized in that the concentration of glycerine in the composition is of 2% to 15% by weight.

25. Pharmaceutical composition, according to claim 1, characterized in that said composition comprises an amount of alkalizing agent that is sufficient to the pH adjustment of the composition in the range of 4.5 to 11.

26. Pharmaceutical composition, according to claim 25, characterized in that the amount of alkalizing agent used is sufficient to obtain pH 7.0 in the composition.

27. Pharmaceutical composition, according to any one of claims 25 to 26, characterized in that the alkalizing agent comprises an inorganic base and/or low molecular weight amine.

28. Pharmaceutical composition, according to any one of claims 25 to 27, characterized in that the inorganic base is sodium hydroxide.

29. Pharmaceutical composition, according to any one of claims 25 to 27, characterized in that the low molecular weight amine is triethanolamine.

30. Pharmaceutical composition, according to claim 1, characterized in that said composition comprises an antimicrobial preservative.

31. Pharmaceutical composition, according to claim 30, characterized in that the antimicrobial preservative is methylparaben.

32. Pharmaceutical composition, according to claim 31, characterized in that methylparaben is used at a concentration of 2% by weight.

33. Pharmaceutical composition, according to claim 1, characterized in that said composition comprises a sweetener.

34. Pharmaceutical composition, according to claim 33, characterized in that the sweetener is selected from: saccharin, stevia, aspartame.

35. Use of a pharmaceutically effective amount of anesthetic and gelling agent, characterized in that it is for the

preparation of a pharmaceutical composition having a minimum viscosity of 30 Pa.s, as defined in the preceding claims.

36. Use, according to claim 35, characterized in that the pharmaceutical composition is employed in dental treatment.

37. Use, according to claim 35, characterized in that the pharmaceutical composition is employed in dermatological treatment.

38. A process for obtaining a pharmaceutical composition, characterized in that it comprises the steps of:

xi. Micronizing the local anesthetic(s);

xii. Adding a levigating agent;

xiii. Adding a gelling agent;

xiv. Adding a preservative and a wetting agent;

xv. pH adjusting, through the addition of an alkalizing agent.

39. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the micronization of the anesthetics involves the participation of an organic solvent.

40. Process for obtaining a pharmaceutical composition, according to claim 39, characterized in that the organic solvent used in the micronization of the local anesthetic is selected from: absolute alcohol, acetone, chloroform.

41. Process for obtaining a pharmaceutical composition, according to any one of claims 39 to 40, characterized in that the organic solvent used is evaporated.

42. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the local anesthetic is partially encapsulated in liposomes.

43. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the levigating agent is selected from: white mineral oil, glycerine, propylene glycol, polyethylene glycol 400, castor oil, cotton oil, polysorbate 80.

44. Process for obtaining a pharmaceutical composition, according to claim 43, characterized in that the levigating agent utilized is propylene glycol.

45. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the gelling agent is a carboxyvinyl polymer.

46. Process for obtaining a pharmaceutical composition, according to claim 45, characterized in that the carboxyvinyl polymer is Carbopol 934.

47. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the preservative is methylparaben.

48. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the wetting agent is selected from: glycerine, sorbitol, propylene glycol, PEG 400, or any mixture thereof.

49. Process for obtaining a pharmaceutical composition, according to claim 48, characterized in that the wetting agent utilized is glycerine.

50. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that a sweetener is added.

51. Process for obtaining a pharmaceutical composition, according to claim 50, characterized in that the sweetener is selected from: saccharin, stevia, aspartame.

52. Process for obtaining a pharmaceutical composition, according to claim 38, characterized in that the alkalizing agent comprises an inorganic base or low molecular weight amine.

53. Process for obtaining a pharmaceutical composition, according to claim 52, characterized in that the inorganic base is sodium hydroxide.

54. Process for obtaining a pharmaceutical composition, according to claim 52, characterized in that the low molecular weight amine is triethanolamine.

55. Product, characterized in that it comprises a pharmaceutical composition as defined in any one of claims 1 to 34.

56. Method of pain treatment, characterized in that it comprises the application of a pharmaceutical composition as defined in any one of claims 1 to 34 to a person who is in need of said treatment.

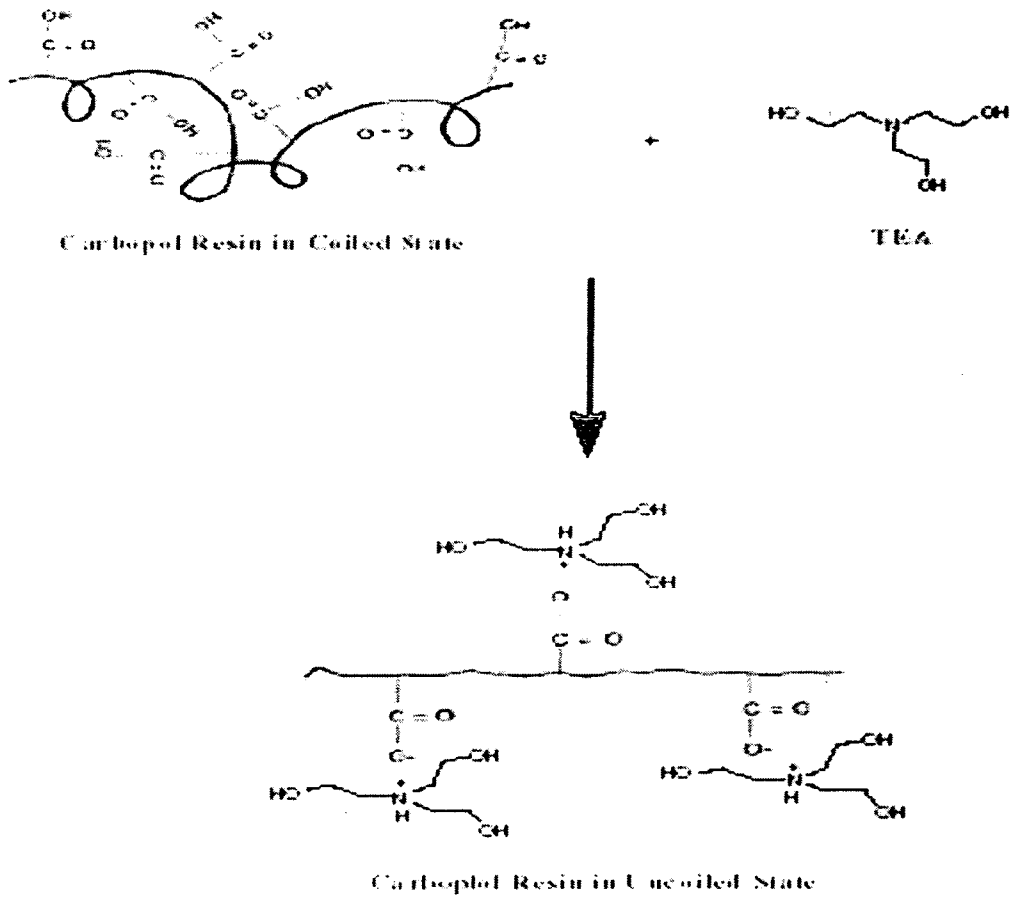
Carbopol Resin in Coiled State
TEA
Carbopol Resin in Uncoiled State

FIG. 1

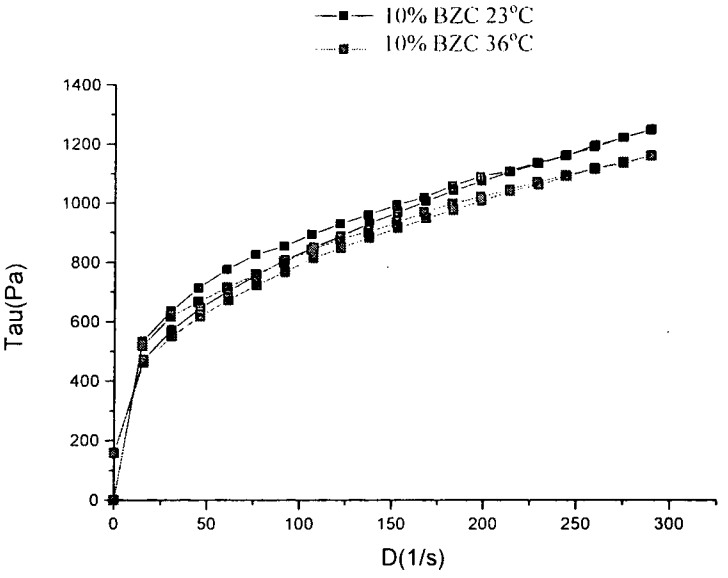
10% BZC 23°C
10% BZC 36°C
Tau(Pa)
D(1/s)
0
200
400
600
800
1000
1200
1400
0
50
100
150
200
250
300

FIG. 2A

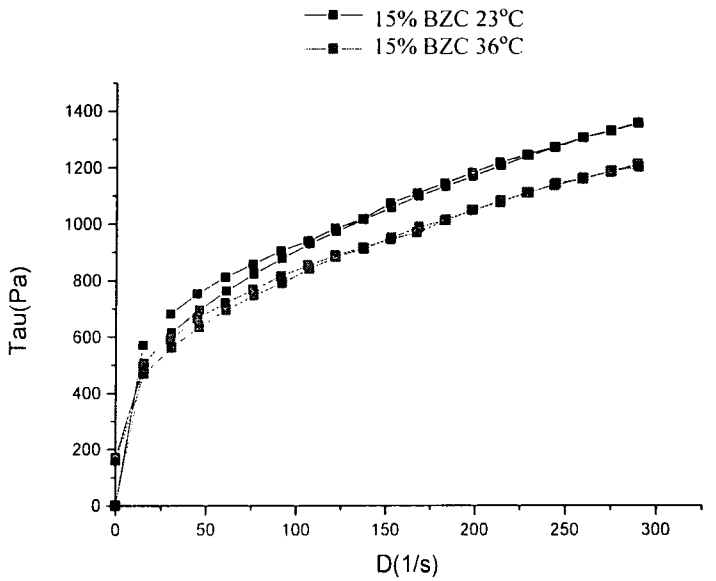
15% BZC 23°C
15% BZC 36°C
Tau(Pa)
D(1/s)
0
200
400
600
800
1000
1200
1400
0
50
100
150
200
250
300

FIG. 2B

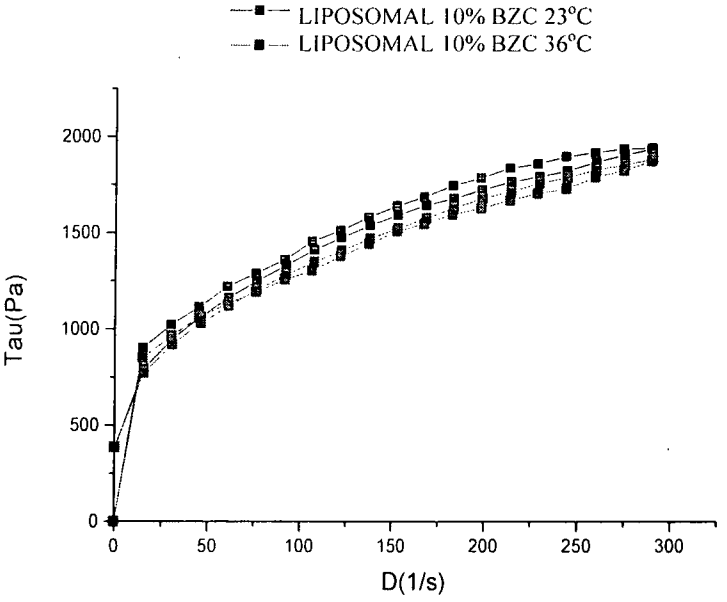
LIPOSOMAL 10% BZC 23°C
LIPOSOMAL 10% BZC 36°C
Tau(Pa)
D(1/s)
0
500
1000
1500
2000
0
50
100
150
200
250
300

FIG. 3A

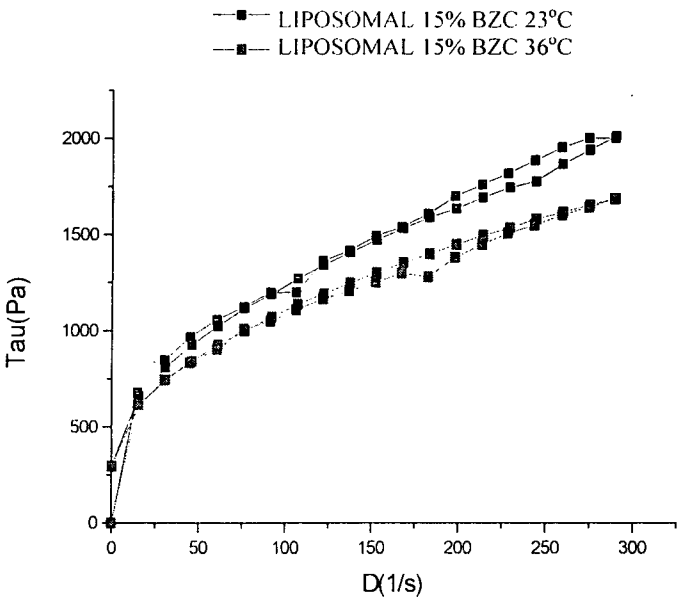
LIPOSOMAL 15% BZC 23°C
LIPOSOMAL 15% BZC 36°C
Tau(Pa)
D(1/s)
0
500
1000
1500
2000
0
50
100
150
200
250
300

FIG. 3B

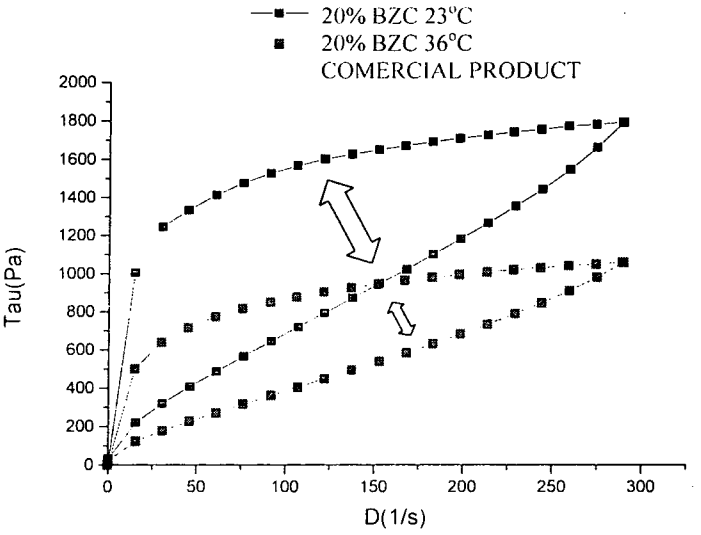
20% BZC 23°C
20% BZC 36°C
COMERCIAL PRODUCT
Tau(Pa)
D(1/s)
0
200
400
600
800
1000
1200
1400
1600
1800
2000
0
50
100
150
200
250
300

FIG. 4

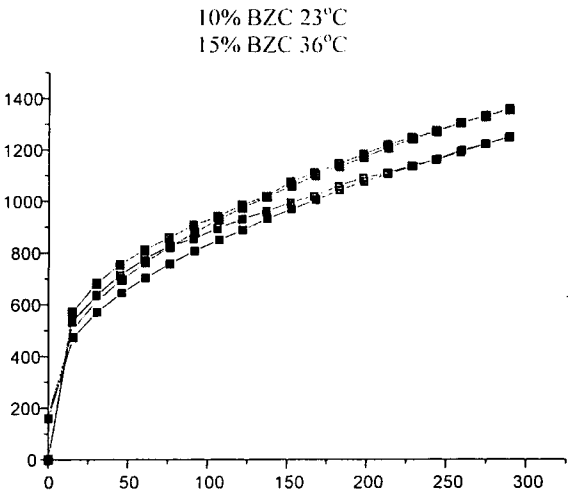
10% BZC 23°C
15% BZC 36°C
0
200
400
600
800
1000
1200
1400
0
50
100
150
200
250
300

FIG. 5A

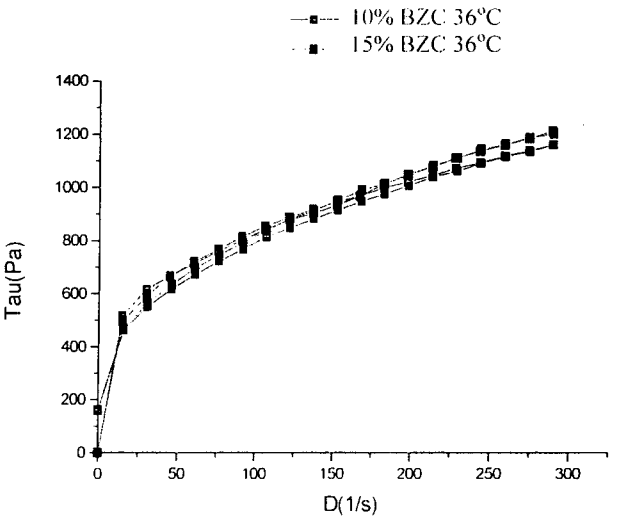
10% BZC 36°C
15% BZC 36°C
Tau(Pa)
D(1/s)
0
200
400
600
800
1000
1200
1400
0
50
100
150
200
250
300

FIG. 5B

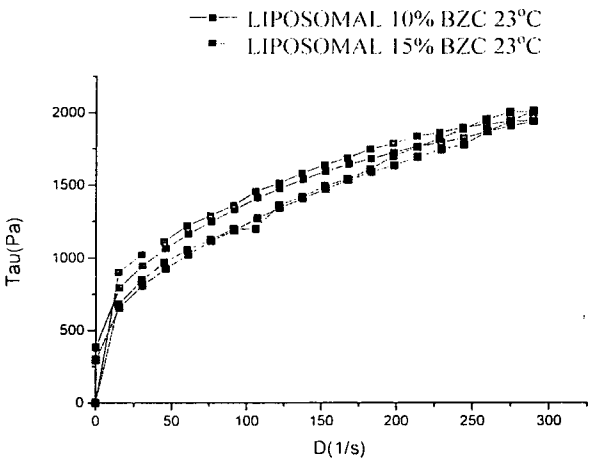
LIPOSOMAL 10% BZC 23°C
LIPOSOMAL 15% BZC 23°C
Tau(Pa)
D(1/s)
0
500
1000
1500
2000
0
50
100
150
200
250
300

FIG. 6A

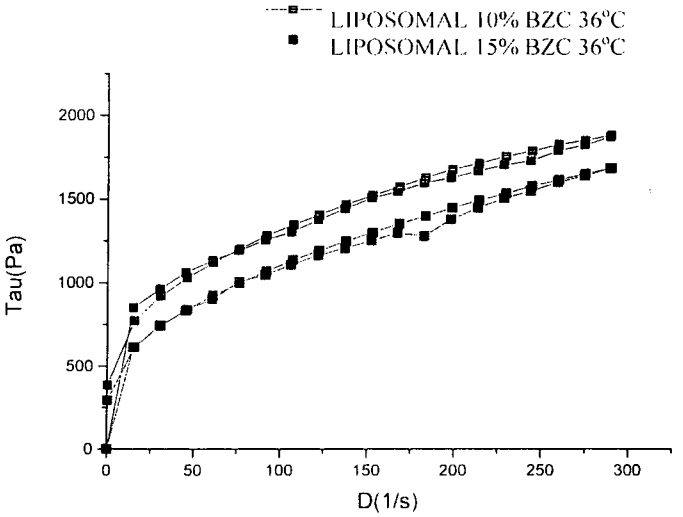
LIPOSOMAL 10% BZC 36°C
LIPOSOMAL 15% BZC 36°C
Tau(Pa)
D(1/s)
0
500
1000
1500
2000
0
50
100
150
200
250
300

FIG. 6B

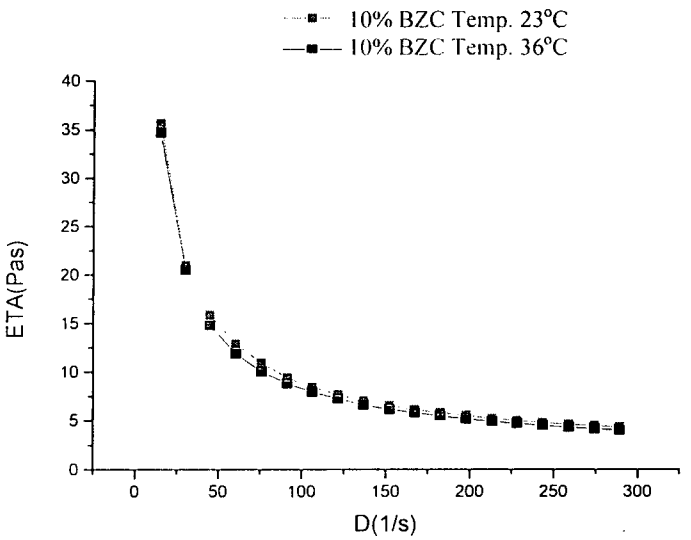
10% BZC Temp. 23°C
10% BZC Temp. 36°C
ETA(Pas)
D(1/s)
0
5
10
15
20
25
30
35
40
0
50
100
150
200
250
300

FIG. 7A

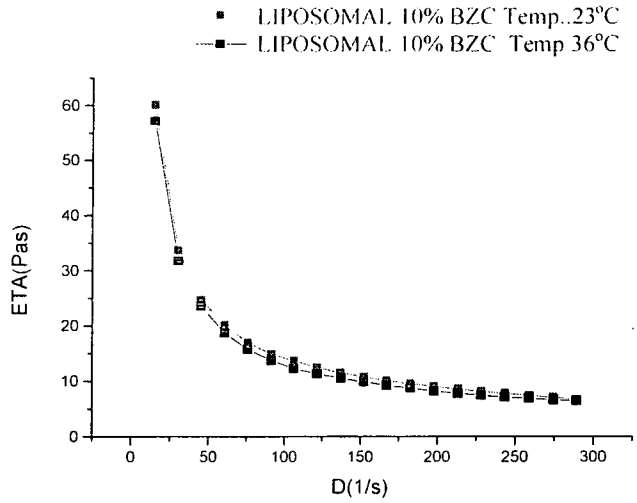
LIPOSOMAL 10% BZC Temp..23°C
LIPOSOMAL 10% BZC Temp 36°C
ETA(Pas)
D(1/s)
0
10
20
30
40
50
60
0
50
100
150
200
250
300

FIG. 7B

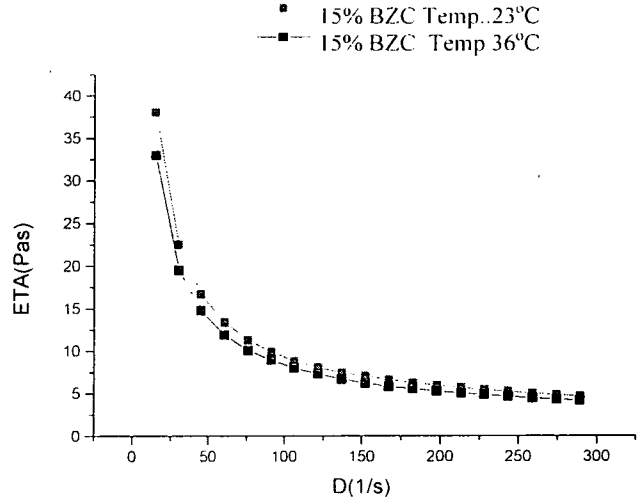
15% BZC Temp..23°C
15% BZC Temp 36°C
ETA(Pas)
D(1/s)
0
5
10
15
20
25
30
35
40
0
50
100
150
200
250
300

FIG. 7C

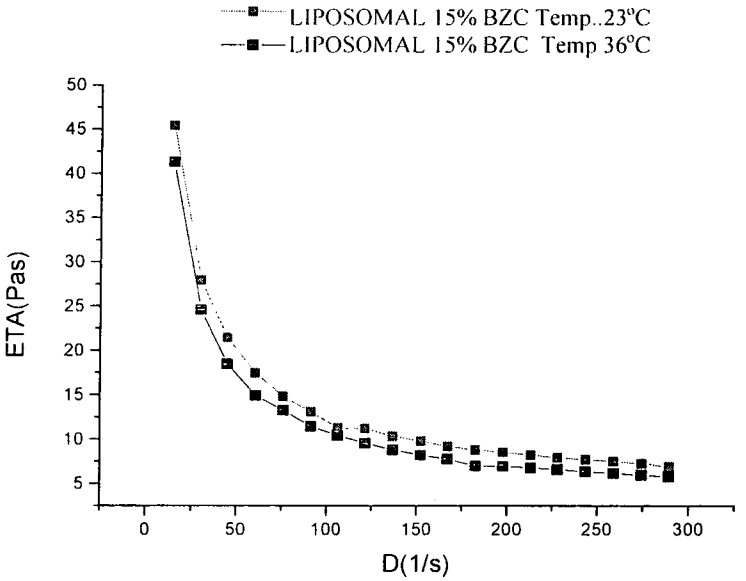
LIPOSOMAL 15% BZC Temp..23°C
LIPOSOMAL 15% BZC Temp 36°C
ETA(Pas)
D(1/s)
50
45
40
35
30
25
20
15
10
5
0
50
100
150
200
250
300

FIG. 7D

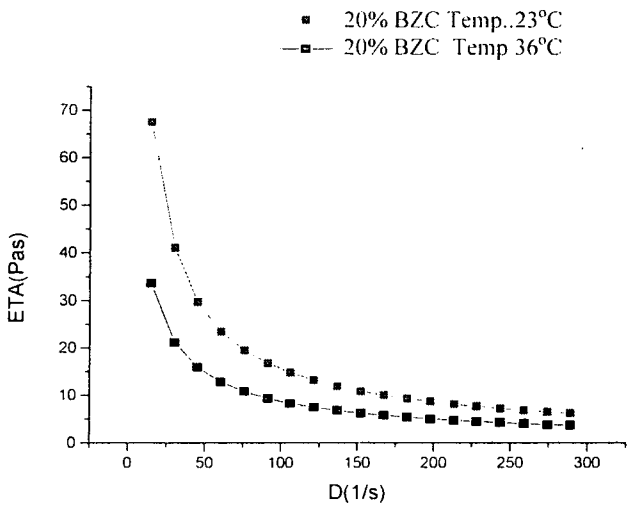
20% BZC Temp..23°C
20% BZC Temp 36°C
ETA(Pas)
D(1/s)
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300

FIG. 8

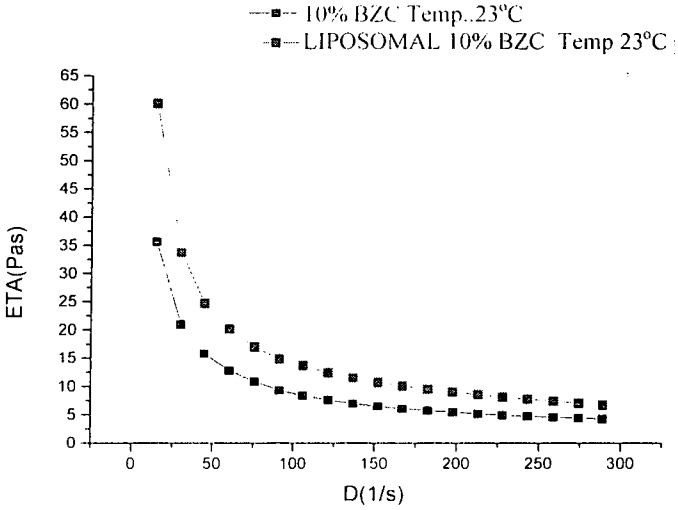
10% BZC Temp..23°C
LIPOSOMAL 10% BZC Temp 23°C
ETA(Pas)
D(1/s)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
0
50
100
150
200
250
300

FIG. 9A

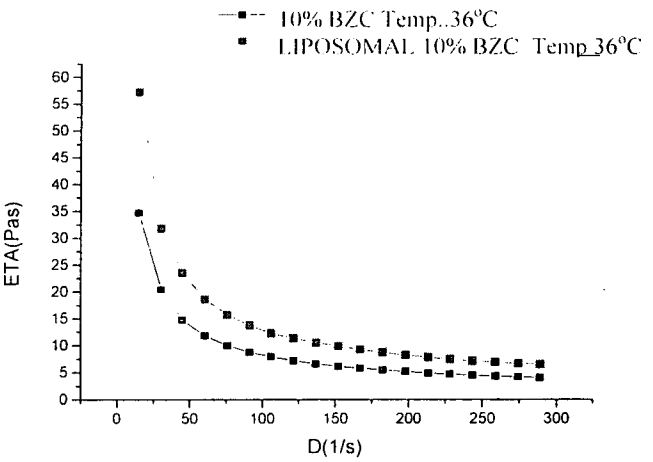
10% BZC Temp..36°C
LIPOSOMAL 10% BZC Temp 36°C
ETA(Pas)
D(1/s)
0
5
10
15
20
25
30
35
40
45
50
55
60
0
50
100
150
200
250
300

FIG. 9B

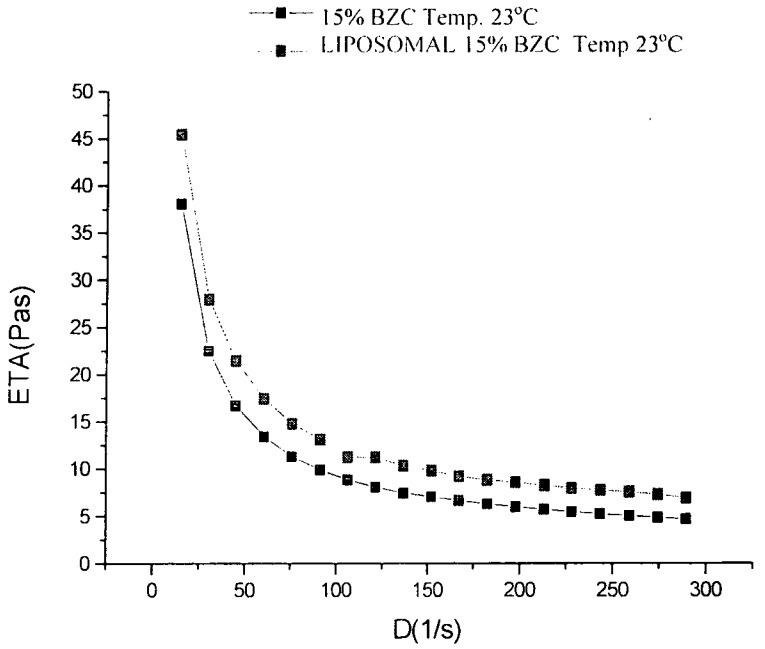
15% BZC Temp. 23°C
LIPOSOMAL 15% BZC Temp 23°C
ETA(Pas)
D(1/s)
0
5
10
15
20
25
30
35
40
45
50
0
50
100
150
200
250
300

FIG. 9C

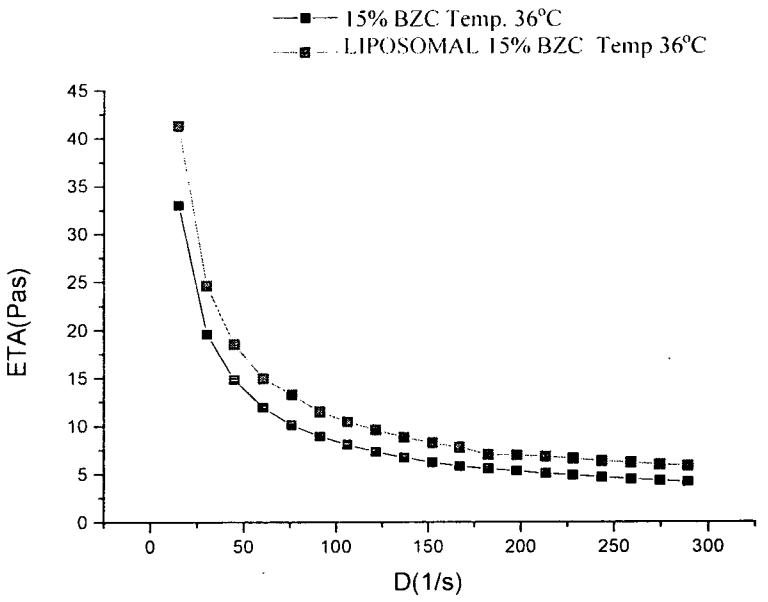
15% BZC Temp. 36°C
LIPOSOMAL 15% BZC Temp 36°C
ETA(Pas)
D(1/s)
0
5
10
15
20
25
30
35
40
45
0
50
100
150
200
250
300

FIG. 9D

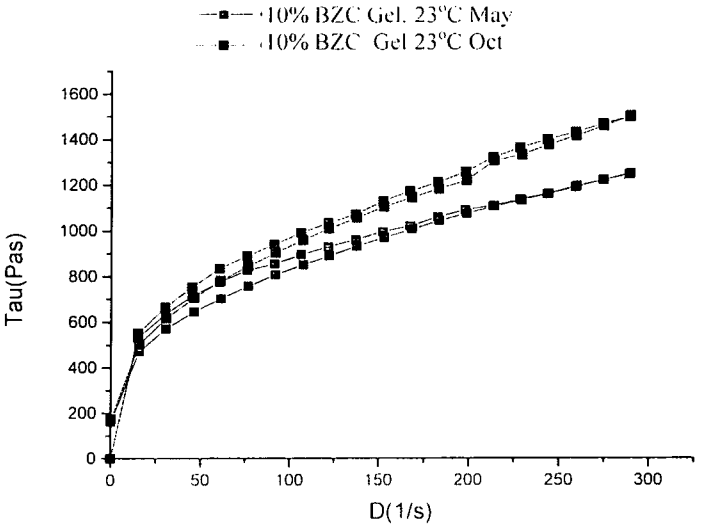

FIG. 10A

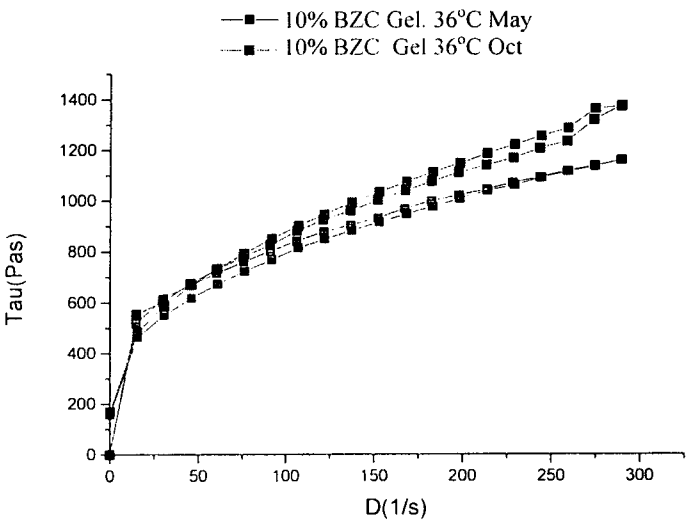

FIGURA 10B

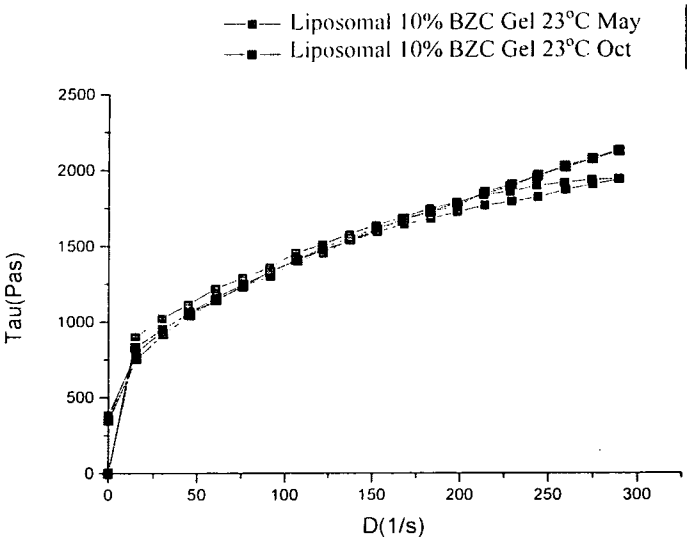

FIG. 10C

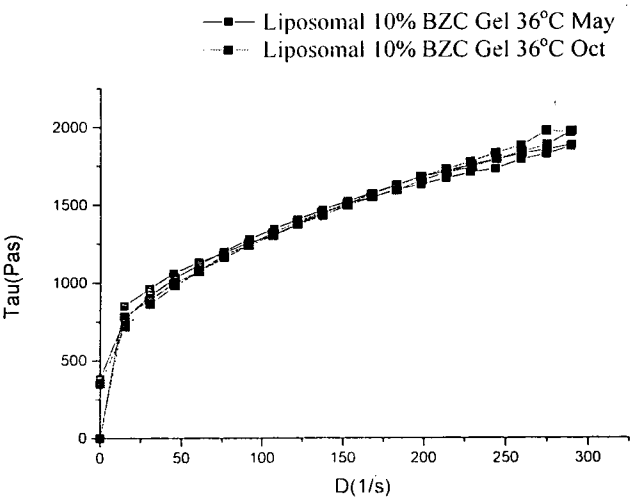

FIG. 10D

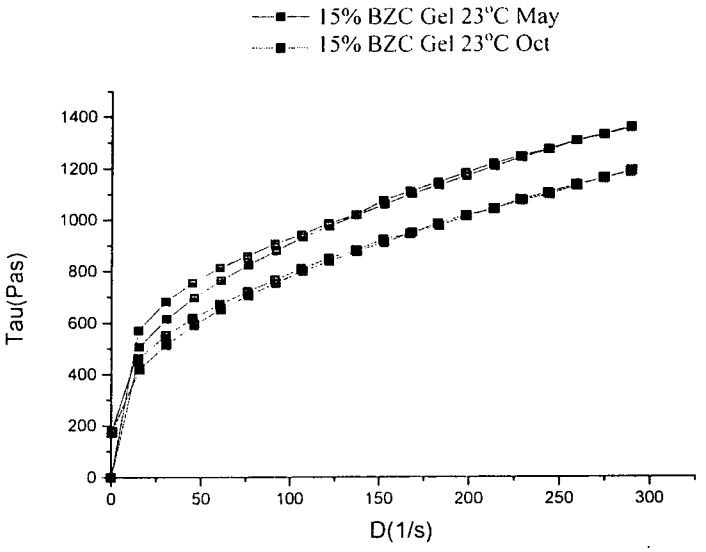

FIG. 10E

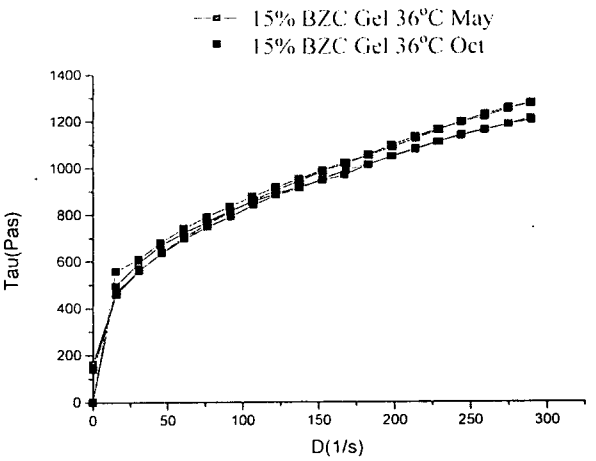

FIG. 10F

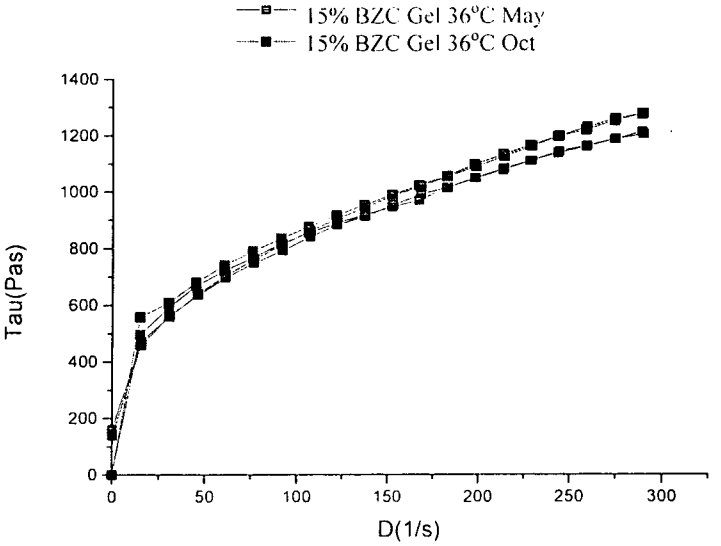

FIG. 10G

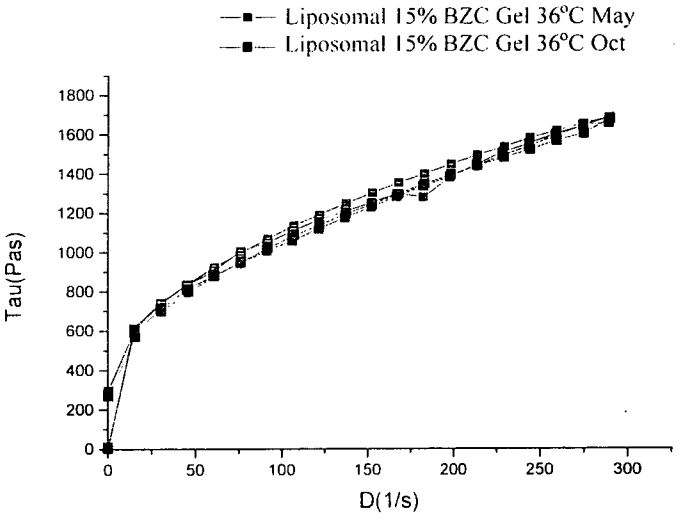

FIG. 10H

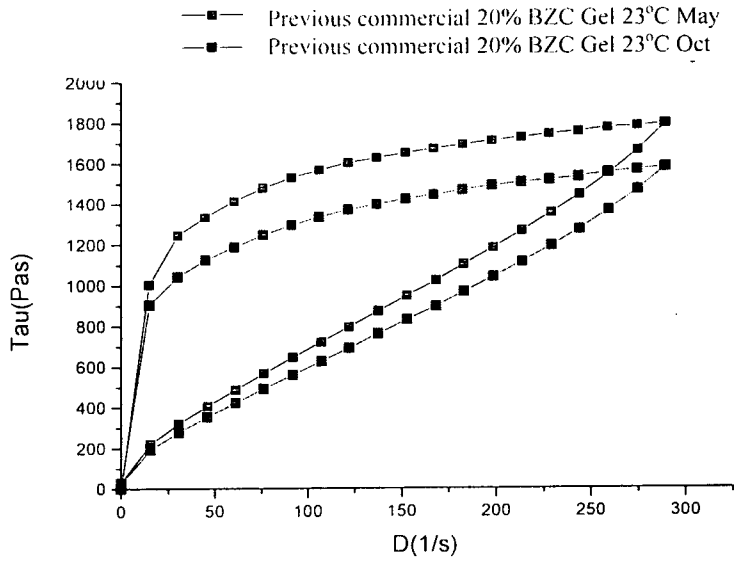

FIG. 10I

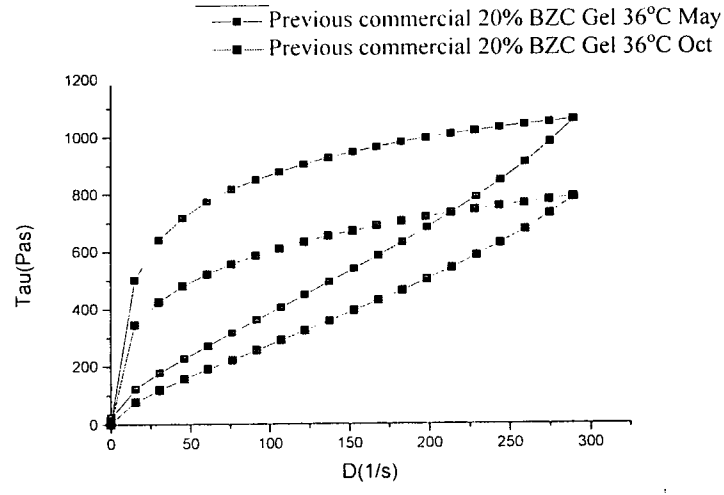

FIG. 10J

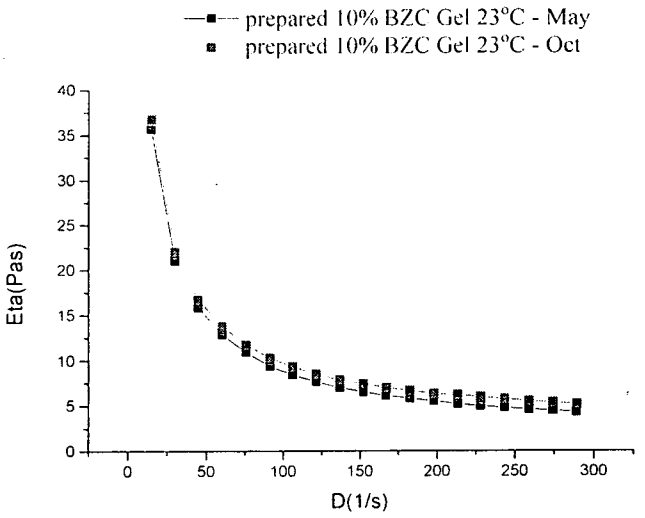

FIG. 11A

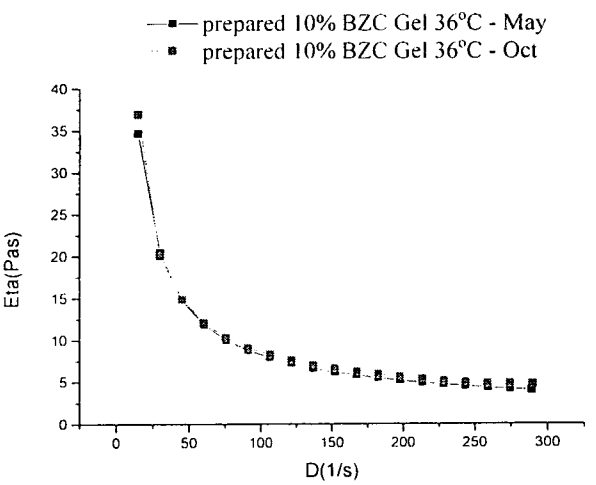

FIG. 11B

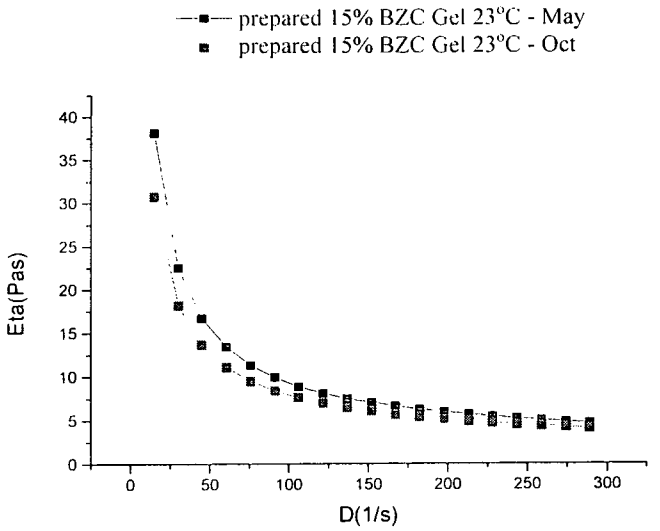

FIG. 11C

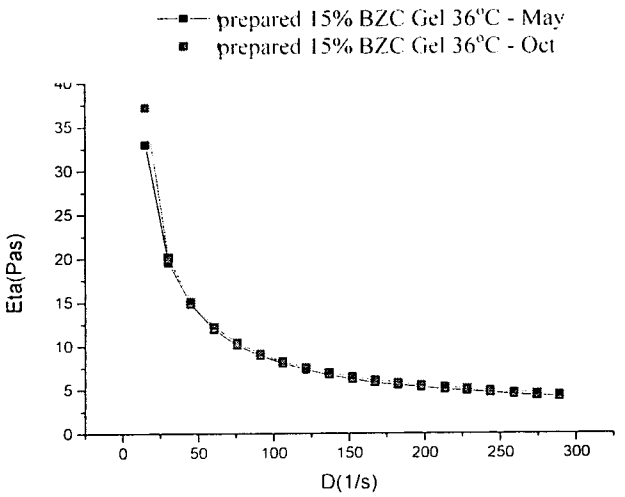

FIG. 11D

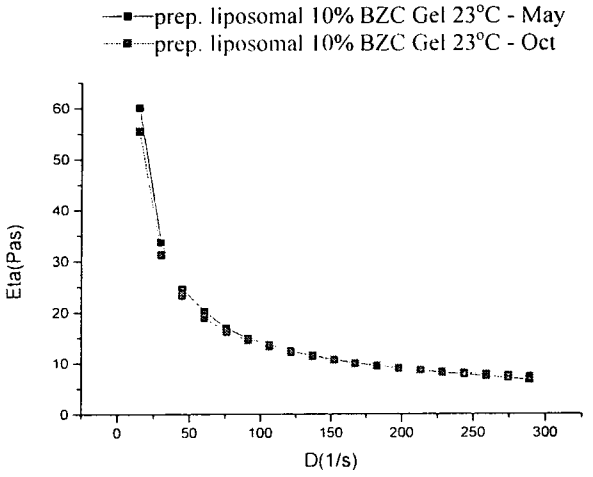

FIG. 11E

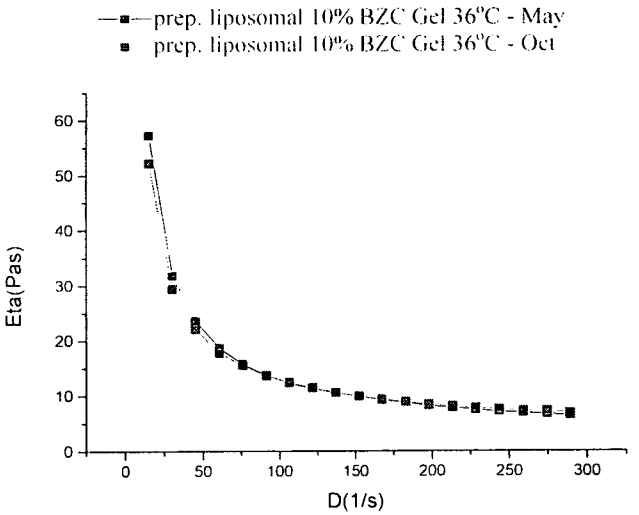

FIG. 11F

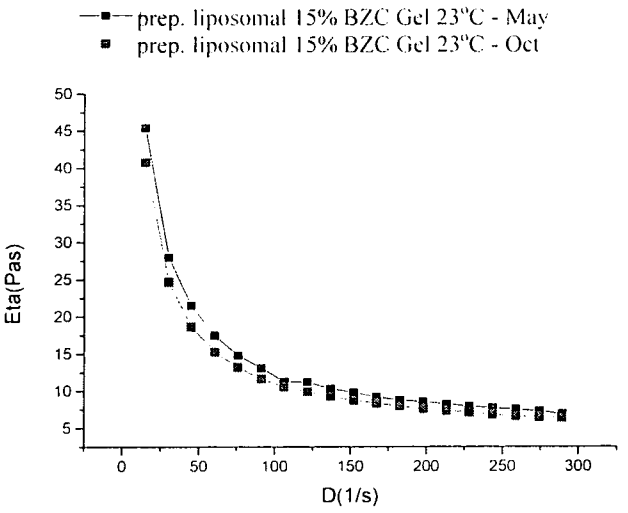

FIG. 11G

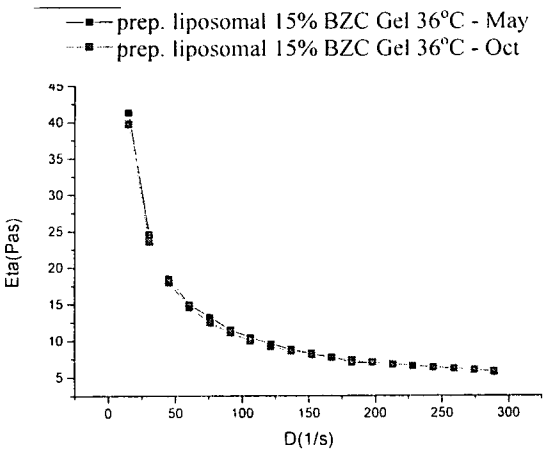

FIG. 11H

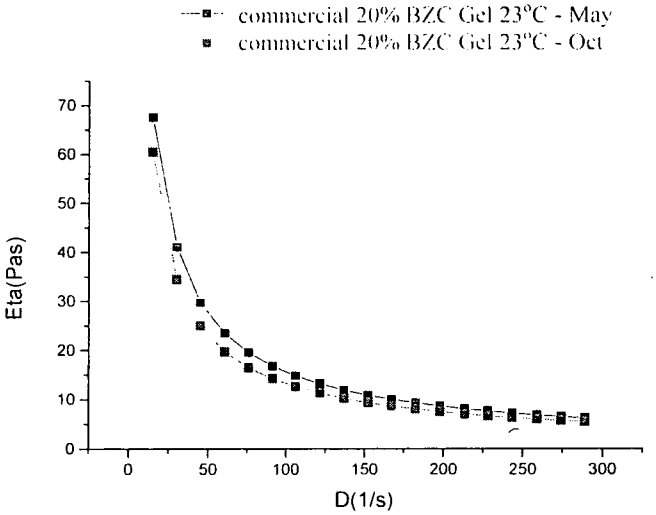

FIG. 11I

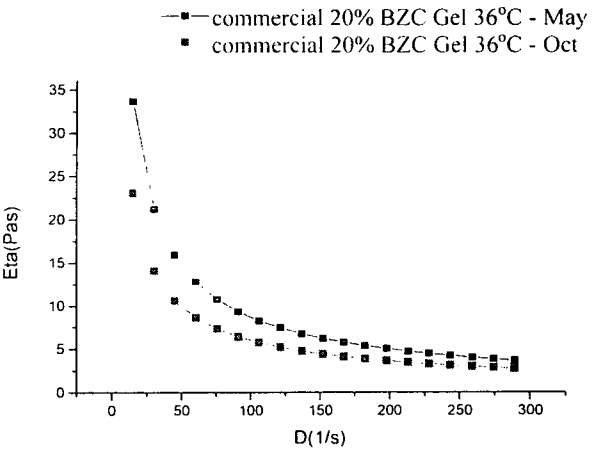

FIG. 11J

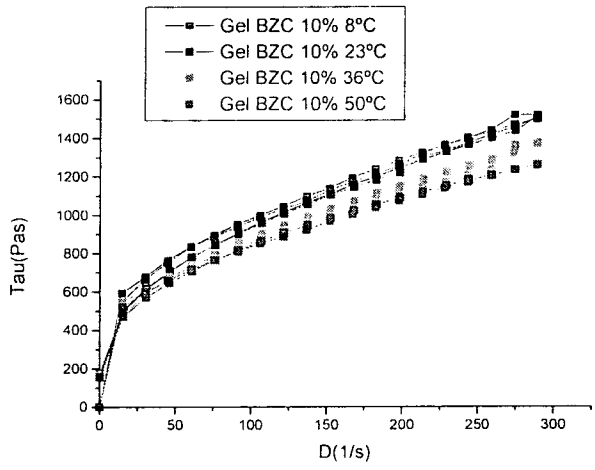

FIG. 12A

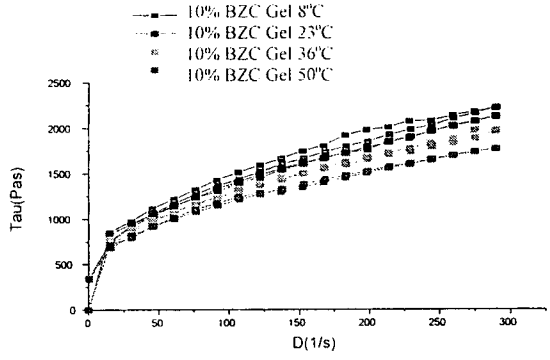

FIG. 12B

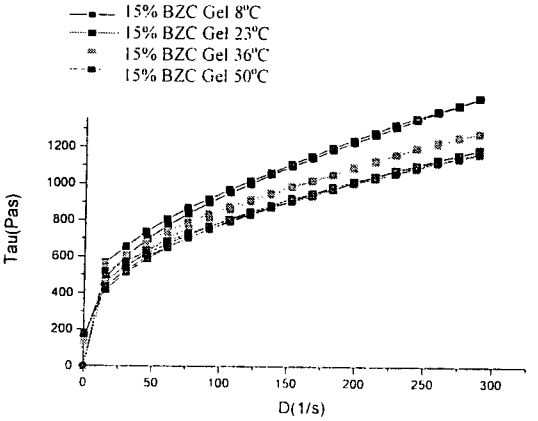

FIG. 12 C

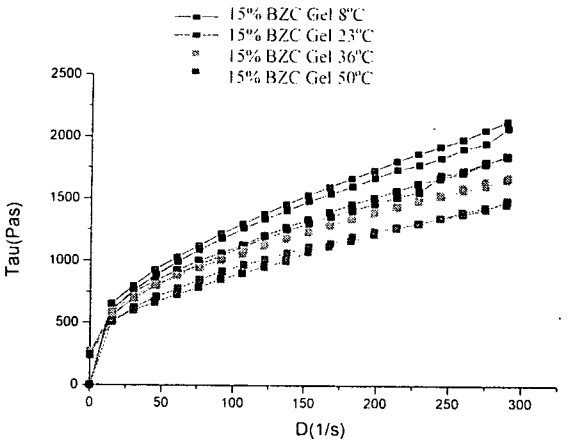

FIG. 12D

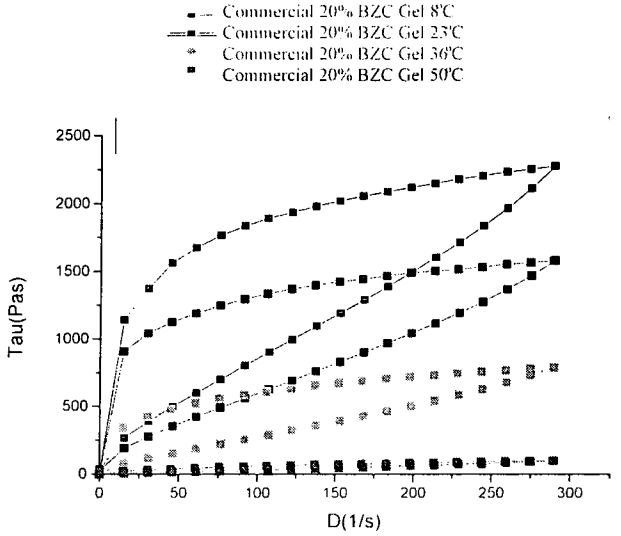

FIG. 12E

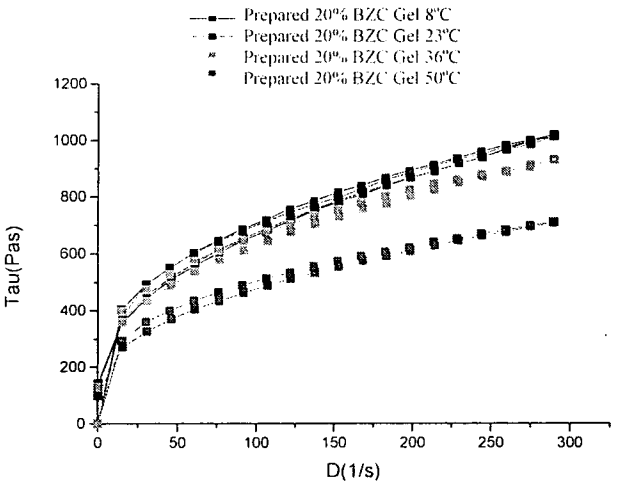

FIG. 12F

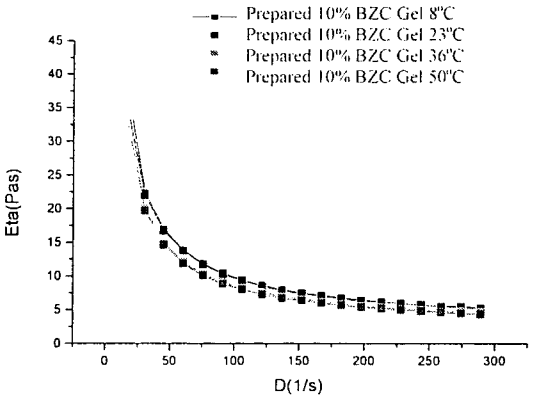

FIG. 13A

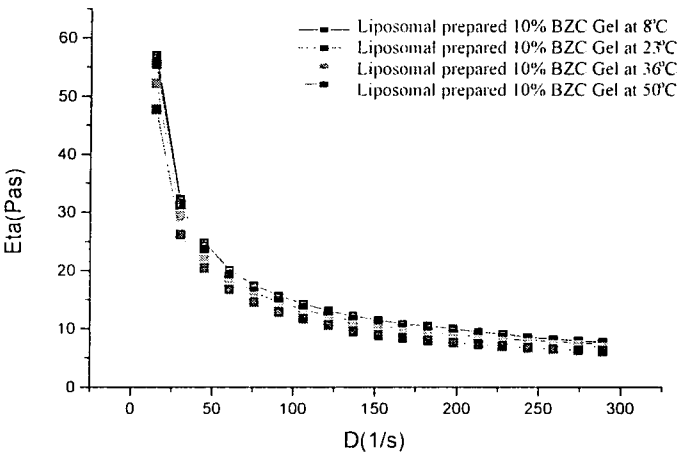

FIG. 13B

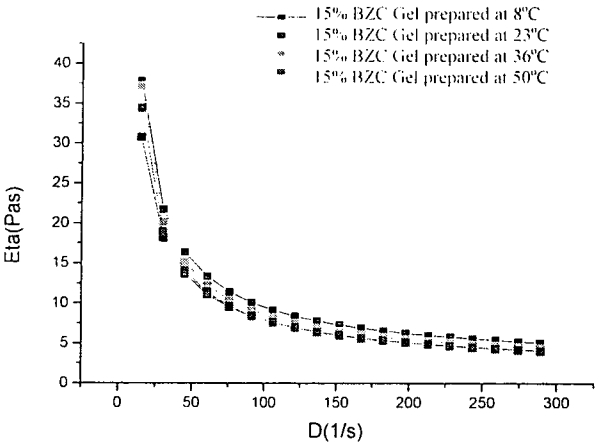

FIG. 13C

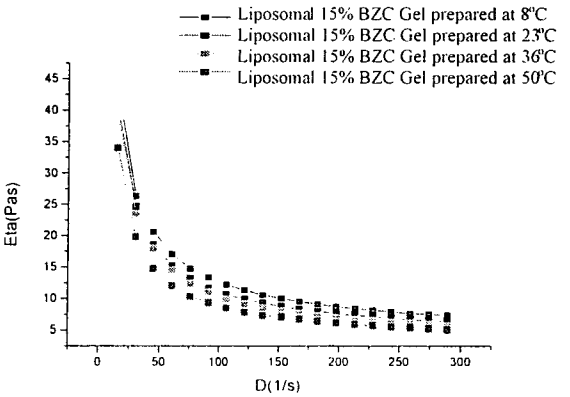

FIG. 13D

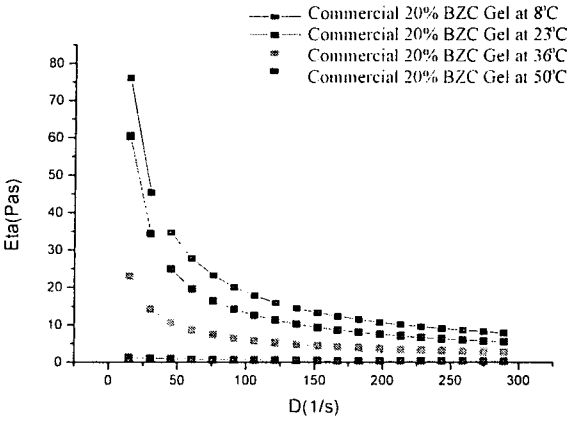

FIG. 13E

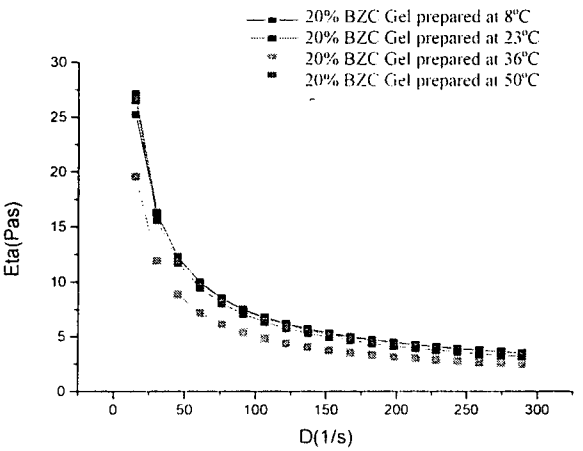

FIG. 13F

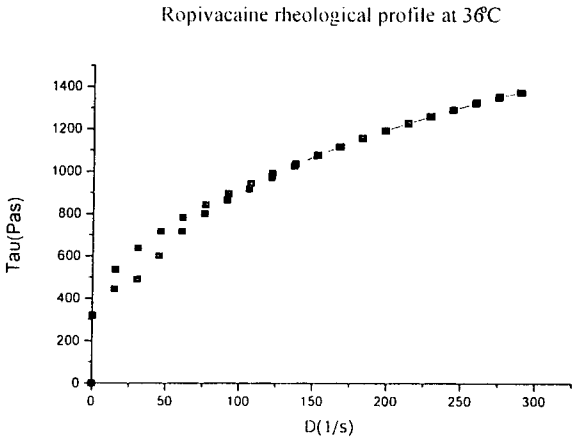

FIG. 14A

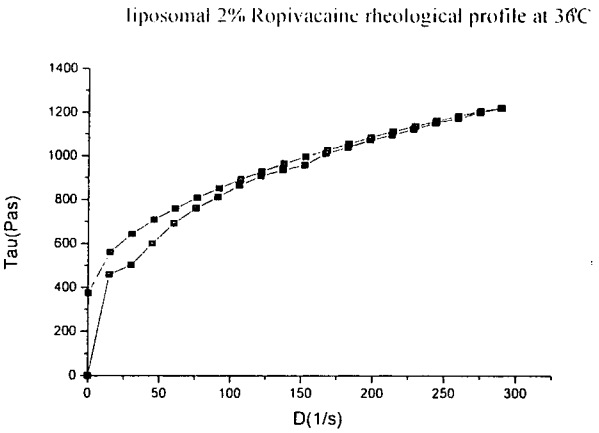

FIG. 14B

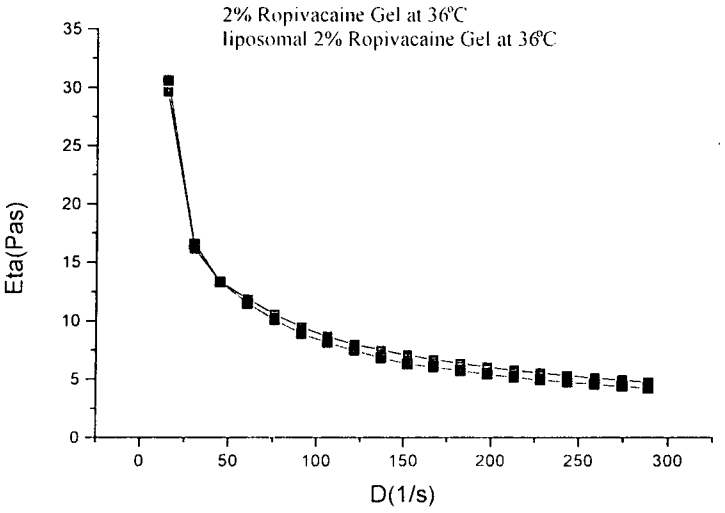

FIG. 15

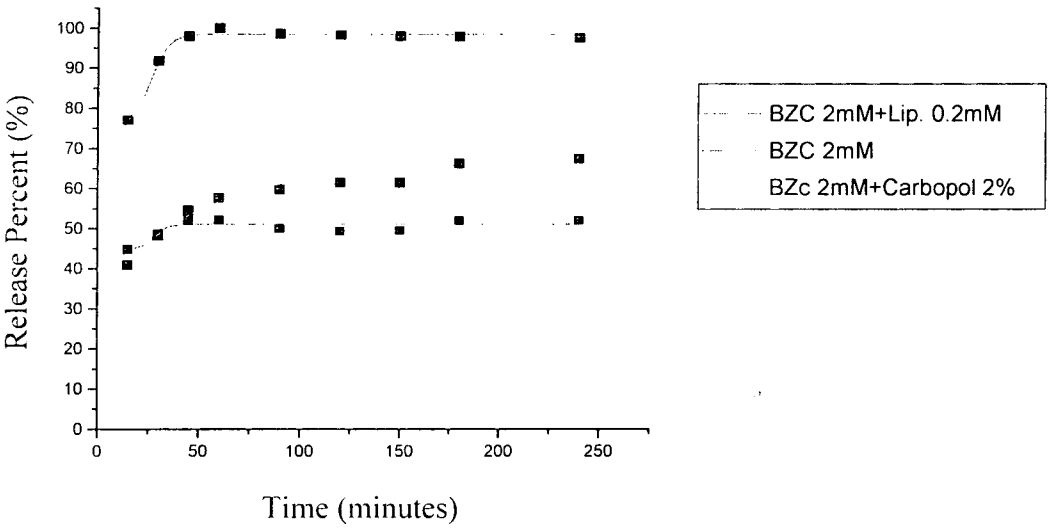

FIGURE 16

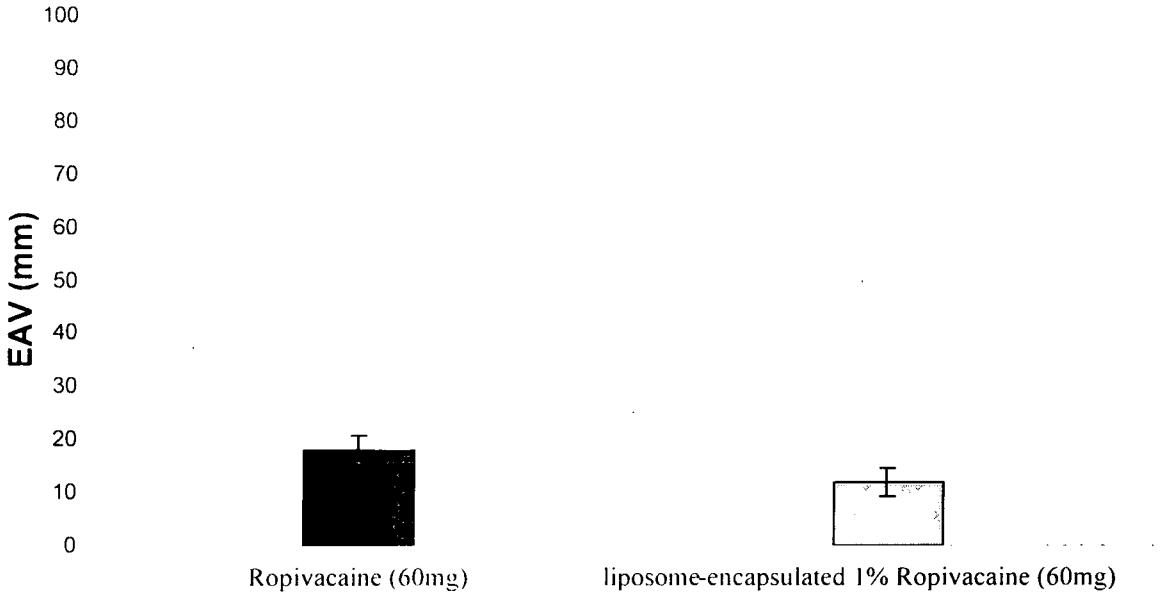
EAV (mm)
100
90
80
70
60
50
40
30
20
10
0
Ropivacaine (60mg)
liposome-encapsulated 1% Ropivacaine (60mg)

FIG. 17

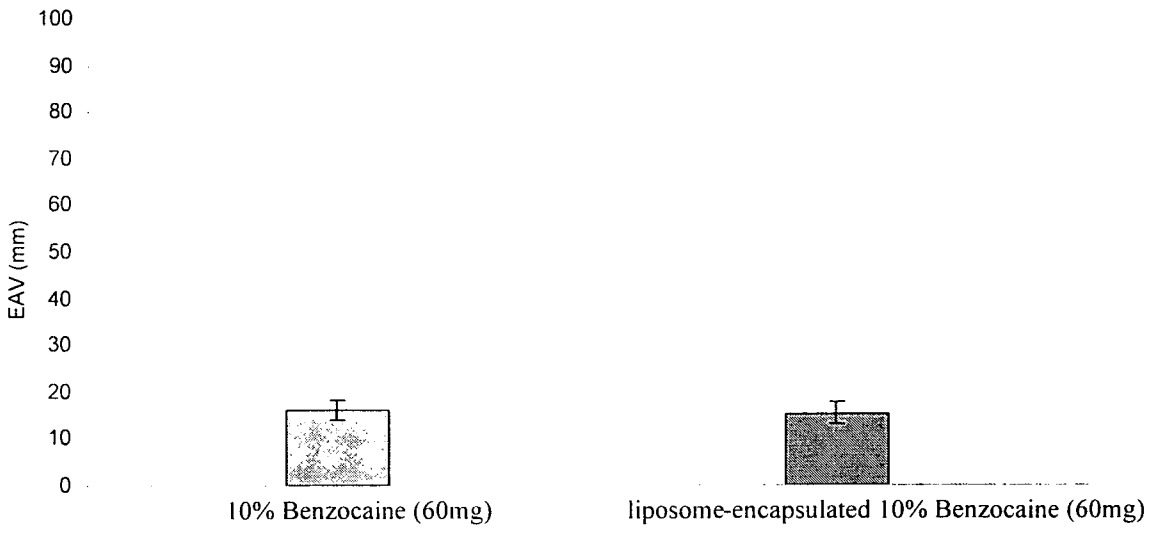
EAV (mm)
100
90
80
70
60
50
40
30
20
10
0
10% Benzocaine (60mg)
liposome-encapsulated 10% Benzocaine (60mg)

FIG. 18

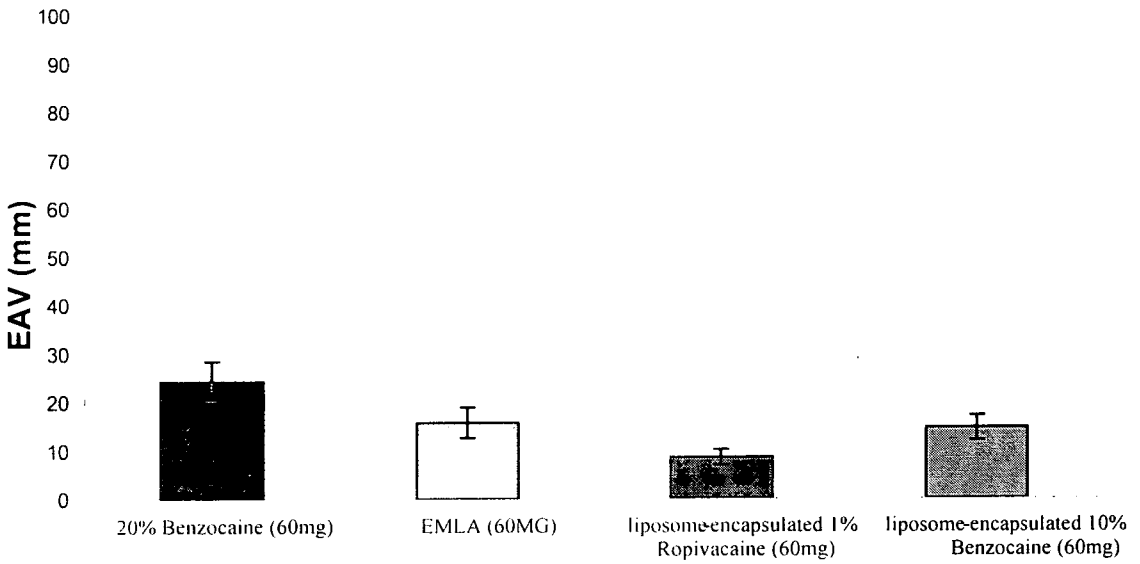
EAV (mm)
100
90
80
70
60
50
40
30
20
10
0
20% Benzocaine (60mg)
EMLA (60MG)
liposome-encapsulated 1% Ropivacaine (60mg)
liposome-encapsulated 10% Benzocaine (60mg)

FIG. 19

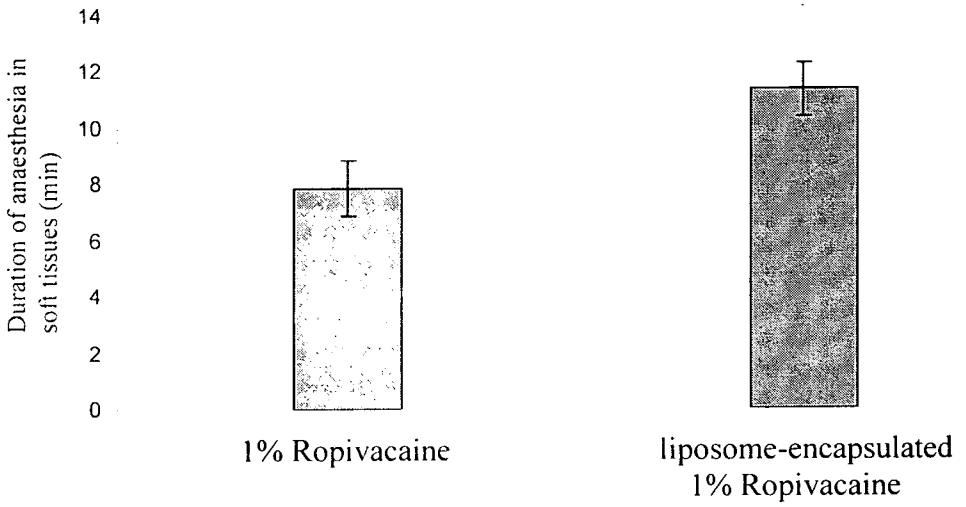
Duration of anaesthesia in soft tissues (min)
14
12
10
8
6
4
2
0
1% Ropivacaine
liposome-encapsulated 1% Ropivacaine

FIG. 20

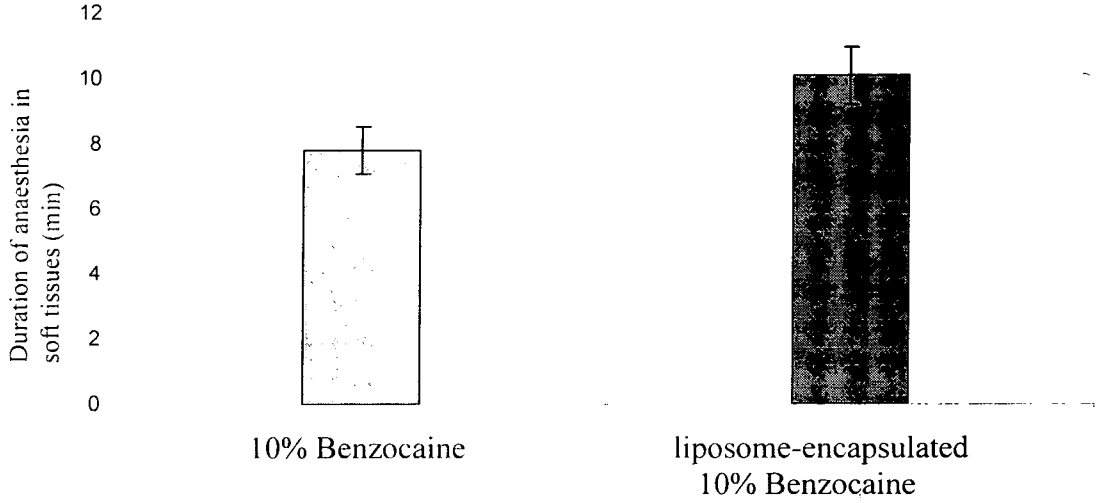
Duration of anaesthesia in soft tissues (min)
12
10
8
6
4
2
0
10% Benzocaine
liposome-encapsulated 10% Benzocaine

FIG. 21

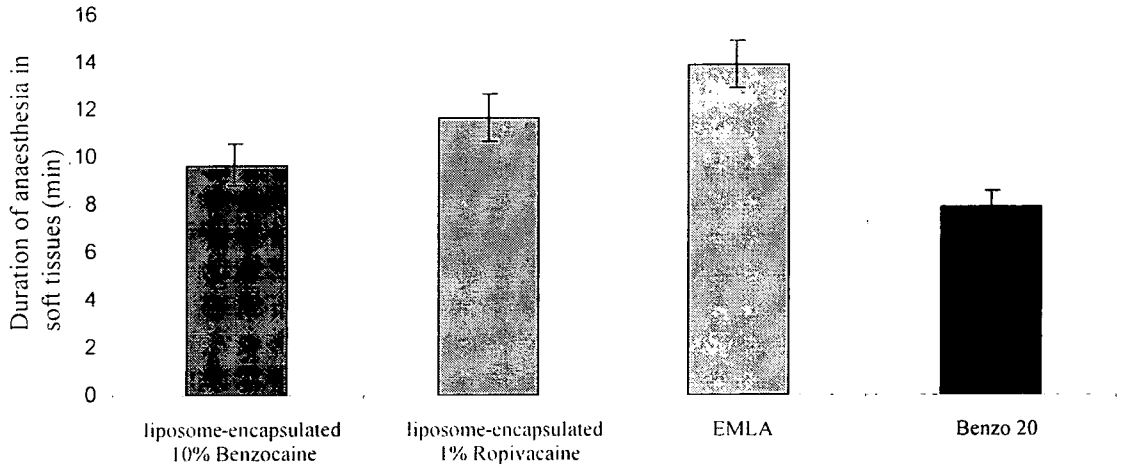
Duration of anaesthesia in soft tissues (min)
16
14
12
10
8
6
4
2
0
liposome-encapsulated 10% Benzocaine
liposome-encapsulated 1% Ropivacaine
EMLA
Benzo 20

FIG. 22