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Review

Thixotropic property in pharmaceutical formulations

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ABSTRACT

This review focuses on the characterization of the thixotropic property, the factors affecting the thixotropic property and its pharmaceutical applications. These factors include pH, temperature, polymer concentrations, polymer modification, polymer combinations, and addition of cations or excipients. The relationships between the rheological properties of thixotropic formulations, and their effects on the controlled drug delivery through various routes including oral, topical, ophthalmic, dental and mucosal administration and pharmacological efficacies were also discussed. The comprehensive analysis of rheological and mechanical properties will provide an insight into the potential usage of thixotropic formulations as drug delivery systems.

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1. Introduction

The flow properties influence each step of the pharmaceutical development process, such as filling, mixing, packing and removal from the container before the application to the action site, and define their in vivo behavior [1]. The time-dependent change in viscosity provides pharmaceutical formulations with the flexible rheological manifestation, which subsequently affects the release profiles of loaded drugs. Therefore, it is essential for pharmaceutical scientists to outline the flow properties and influencing factors, and their effects on the pharmacological efficacy of thixotropic formulations, especially emulsions, ointments, colloids and gels.

2. Rheology and thixotropy

The study on the flow properties of matter and its deformation are termed as Rheology which constitutes an integral branch of physics, physiology and pharmaceutical fields. There are two extremes of rheological behavior: i) elastic behavior—which refers to the ability of a formulation to restore its original shape when the external force is removed, ii) viscous (or plastic) behavior, which is known as a property of ideal Newtonian liquids, where any deformation ceases when the applied force is removed [2]. Most viscoelastic materials lie in between elastic and viscous behavior, and their micro-structural systems control both viscosity and elasticity in response to different flows [3]. The structure of an emulsion or polymer is governed by the random distribution of droplets or the degree of entanglement, respectively. The maximum structure is observed when the distribution is symmetric at most, which subsequently ensues the maximum viscosity and elasticity, whereas the minimum structure is observed when the distribution is as asymmetric as possible relative to the flow [4].

Viscosity represents the resistance to the relative motion of adjacent liquid layers and the reciprocal of viscosity is termed as fluidity. The viscosity of the fluid varies with the shear stress and the consistency depends upon the duration and rate of shear (Fig. 1). The time-dependent change in viscosity is the desired property in the pharmaceutical formulations due to their requirement of the flexibility in drug delivery [5]. If the rheological manifestation of viscosity-induced structural changes is reversible and time-dependent, the effect is called thixotropy. The difference between thixotropical and shear-thinning behavior is only that of the time for the structure to regroup during shear or at rest. When a material is shear-thinning it changes the micro-structure instantly, whereas for a thixotropic material it takes some time. At present, shear-thinning materials also are considered as thixotropic since it always takes time, even though limited, to regroup the micro-structural elements.

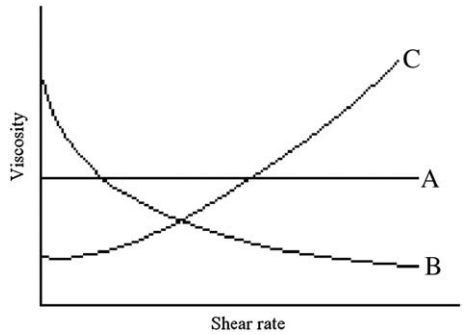

Fig. 1. Effect of shear rate on the viscosity of (A) Newtonian liquids, (B) shear-thinning systems and (C) shear thickening systems.

Due to the wide range of applications of the thixotropic properties in the field of pharmacy, formulations in particular, it is essential to understand this complex phenomenon utilized in the advanced formulations.

3. Definition of thixotropy

The word thixotropy, which was first introduced by Freundlich in the book "Thixotropie" [6], is put together by the two Greek words "thixis" (stirring, shaking) and "trepo" (turning, changing). According to the Swedish National Encyclopedia (1989–1996) [7], thixotropy is defined as "property of viscous (viscid) or get-like product turning more liquid as the longer time and the more vigorous it is deformed (e.g. by stirring)." It is generally accepted that thixotropy is the phenomenon of the fluid which shows a reversible structural transition (i.e., gel–sol–gel conversion) due to the time-dependent changes in the viscosity induced by temperature, pH or other components without any changes in the volume of the system [8]. In other words, thixotropy is a term to describe an isothermal system in which the apparent viscosity decreases under shear stress, followed by a gradual recovery when the stress is removed.

A thixotropic material becomes more fluid as the duration of applied forces, such as stirring, pumping or shaking, increases (i.e., the work softening process) (Fig. 2). It is reversible, so that if left undisturbed for some time thixotropic material regains its viscosity. A rheopectic material becomes more viscous as the duration of applied force increases, which is known as the work hardening process, the opposite of thixotropy [9].

4. Characterization of thixotropy

A system was considered as either a Newtonian flow or non-Newtonian flow depending on whether viscosity is correlated with the shear rate or the composition of the liquid. The liquids that follow Newtonian flow include water, ethanol, benzene, ethyl ether, glycerin and castor oil, whereas most thixotropic fluids, such as ointments, pastes, putties and clays, are examples of non-Newtonian materials [10].

4.1. Newtonian systems

A system is said to have Newtonian flow behavior when its viscosity is independent of shear rate and dependent upon the composition of the liquid, temperature and pressure. It is observed that viscosity decreases as the temperature increases, whereas it increases with an increase in pressure [1,2].

The graphs representing the flow properties are termed as Rheograms and in case of Newtonian systems the flow curves (shear stress vs. shear rate) are straight lines passing through origin, indicating that shear stress (τ) or the force per unit area (F/A) varies directly with the shear rate as described in the following equations.

$$\tau = F/A = \dot{\eta}D, \text{ where } \dot{\eta} = \text{viscosity and } D = \text{rate of shear}$$

The slope of the line represents viscosity, which is the resistance to the relative motion of adjacent liquid layers and can be obtained by

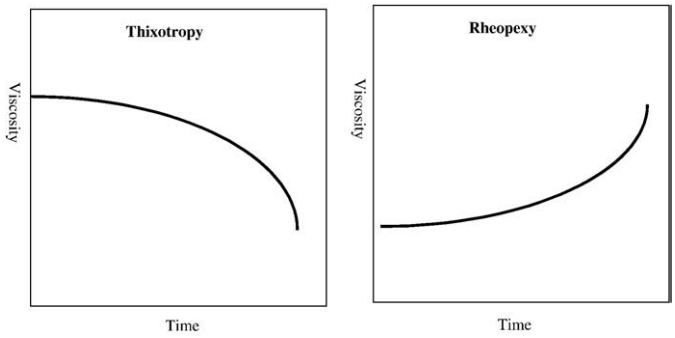

Fig. 2. Thixotropy and rheopexy profiles (viscosity vs. time) (References: [89, 90]).

the tangent of the angle the line makes with the horizontal axis (i.e., a ratio of shear stress over shear rate). The unit of viscosity is Pascal times second (Pa*s).

4.2. Non-Newtonian systems

As the name implies, there is a deviation from Newton's relation between shear stress and the rate of shear. The viscosity of non-Newtonian fluids changes according to the rate of shear, thus non-Newtonian systems have no constant viscosity [1]. non-Newtonian systems can be of three general types, such as plastic, pseudo plastic and dilatants.

In case of plastic materials, it is observed that there is no flow until it reaches the yield value as shown in Fig. 3. When stress above the yield value is applied, they exhibit free flowing liquid nature. Materials exhibiting this type of flow property are also termed as Bingham Bodies [11]. This phenomenon can be attributed to the formation of three-dimensional networks due to concentrated particles in the total volume of the suspensions. An addition of surfactants or deflocculating agents reduces the attraction (Van Der Waals forces) and repulsive (Born forces) forces between particles and hence reduces or eliminates the yield value.

Thixotropy is the property exhibited by the pseudo plastic systems which exhibit the time-dependent change in the viscosity. Thixotropic systems demonstrate a decrease in viscosity with time under the constant shear. An enhancement of shear due to progressive break down of the structure of liquid and further rebuilding of the structure due to Brownian motion, which makes the particles move to their most favorable positions from a structure–entropy perspective, is assumed to be the reason for pseudo plasticity [12].

According to Chemical Terminology, the systems whose viscosity increases with an increase in the rate of shear, as shown in Fig. 2, are called as shear thickening systems (i.e., also known as dilatants) [13]. This property is exhibited by dispersions containing high percentage of small, deflocculated particles, for example: clays, slurries, suspensions of starch in water, aqueous glycerin or ethylene glycol.

5. Measurement of thixotropy

There are a number of ways to quantify the thixotropic behavior of materials; i) measure the area within the hysteresis loop from a shear rate curve, 2) use viscometers or rheometers to assess rheological behavior at varying shear stress and shear rates, 3) use Texture Analyzer to characterize the textural and rheological profiles, and 4) apply the numerical/computer models to assess rheological characteristics of bioadhesive gels.

5.1. Hysteresis loop approach

The most suitable way for the measurement of thixotropy is to describe the material response in shear stress due to an inflicted deformation or a shear rate [14]. The shear rate increased with time until it reaches a maximum shear value. Thereafter, without any disturbance, the process is reversed by decreasing the shear rate, leading to the formation of up and down curves. The area enclosed by the up and down curve is referred to as hysteresis loop (Fig. 2). The down curve will be substantially a straight line in most cases and its slope will be dependent on the rate of thixotropic buildup [15].

A semi-empirical quantitative assessment of thixotropy using the rheograms is not unique but depends on its rheological history (i.e., previous shear or rest conditions, time sweep etc.) and chemical composition [16]. Formulations in incompatible composites tend to produce a structure that is destroyed at high shear rates and that reform on aging at elevated temperatures or excessive pHs. Through hysteresis loop approach, the behavior of the fluid can be demonstrated in terms of simple shear flow and the relation of such behavior to laminar shear flow can be elucidated. The hysteresis loop approach is at present the most widely used method and was successfully utilized in the studies of the thixotropic behavior of Aerosil 200 hydrogels at different concentrations [17] and carboxymethyl cellulose (CMC) solutions [18].

5.2. Multi-point viscometer approach

Viscometer was used to characterize thixotropic materials [19]. The single-point viscometer could not adequately characterize thixotropic materials as it is required to assess their behavior at varying shear stress and shear rates, necessitating a multi-point viscometer. The advanced rheometers feature both controlled strain and stress modes and equipped with a wide range of options and accessories, representing an ideal research tool to study viscosity fluids.

The falling sphere method based on the multi-point approach is considered to be the most ideal method for non-Newtonian liquids. An automatic controller regulates the shear rate with respect to time and rotational viscometers can continuously assess the shear in the entire fluid. Rotational viscometry was used for the study of the thixotropic properties of commercially available urea-formaldehyde resins from the standpoint of structure, molar mass and molar mass

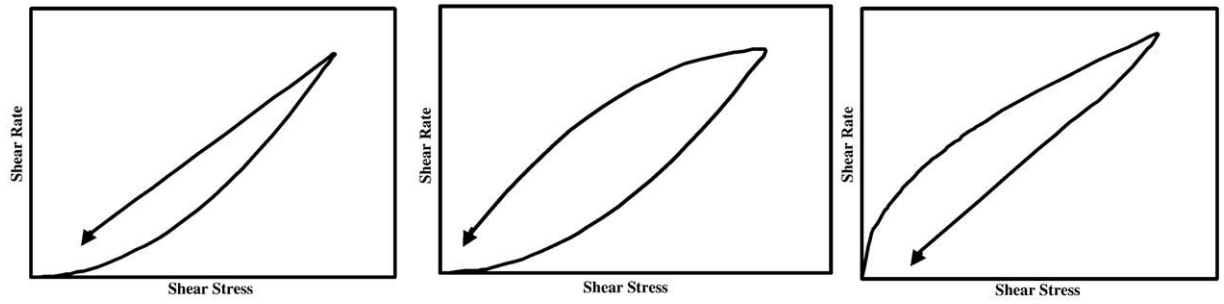

Fig. 3. Thixotropy in pseudo plastic, plastic and dilatant systems (References: [89, 90]).

distribution [20]. The results of the rheokinetic study apprehended the relationships, which are consistent with conceptions about the formation of the resin structure and processes occurring during the initial period of polycondensation, proving that the multi-point viscometer approach is a generally recognized method for rheological measurements of non-Newtonian liquids.

5.3. Texture profile approach

The texture profile analysis has been used to examine the rheological (Viscosity and fluidity) and textural characteristics (Hardness, Compressibility, Adhesiveness, Cohesiveness) of bioadhesive gels [21]. In texture profile analysis, an analytical probe is twice depressed into the sample at a defined rate to a desired depth, allowing a pre-defined recovery period rate between the end of the first and the beginning of the second compressions. From the resultant force–time curve, the mechanical parameters (Hardness, Compressibility, Adhesiveness, Cohesiveness) can be derived using a Stable Micro Systems Texture Analyzer [21,22]. In addition, rheological performance was also evaluated using flow rheometry to quantify general rheological properties of the candidate formulations.

Descriptive analysis was used to quantify the perceived hand texture characteristics of agarose gels, and it was found that linear viscoelastic properties could not distinguish gels as sensitively as fracture properties which were more capable of predicting rheological texture properties [23]. This study has demonstrated not only the applicability of textural analysis for the mechanical characterization of bioadhesive semi-solid gel systems but also the direct influence of viscosity on the mechanical parameters defined by textural analysis.

5.4. Numerical/computer model based approach

The physicodynamic/computer models were presented for the thixotropic measurement of shear-thinning behavior in suspensions [24], magneto- and electro-rheological fluid dampers [25], food hydrocolloids [26] or contracting skeletal muscle [27]. Numerous rheological models (Newtonian, Bingham, Casson, Power law and Herschel-Bulkley) were introduced to describe shear stress and shear behavior [28]. The Herschel-Bulkley equation is preferred to Power law or Bingham relationships, because it results in more accurate models of rheological behavior when adequate experimental data are available [29]. However, the Power law model generally gives a higher correlation coefficient values between viscosity and pH [30].

The thixotropy models established under different local flow conditions and macroscopic flow properties appeared capable of predicting characteristics of transient flows more precisely and constantly than other methods like abrasive flow machining (AFM), and even over times much shorter than in the NMR rheometrical tests [31]. It was also found that a few parameters involved with start flows and blockages might be sufficient to globally characterize the local and macroscopic thixotropic behavior under various conditions.

Usui and coworkers have recently presented the thixotropy model in which the number of primary particles contained in an aggregated cluster was adopted as the model parameter [32]. In the Usui model, inter-particle bonding energy between primary particles was determined when the steady state viscosity data were experimentally given. The simplified Mewis-Denn model, consisted of a modified upper convected Maxwell model, a kinetic equation and five parameters, was also proposed as the thixotropy model [33]. The calculated results showed that the simplified Mewis-Denn model was well capable of describing the reported thixotropy loop experiments of the polymer melt and that the stress deviations between the experiments and predictions were smaller than those obtained using the other methods under the same conditions.

6. The factors affecting thixotropic property

The phenomenon of thixotropy is influenced by several factors like pH, temperature, polymer concentrations, polymer modification or combinations, addition of cations or anions, as described in Table 1. Excipients, such as lecithin, sodium chloride and glycerol, were used to form pseudoplastic formulations.

6.1. pH

Due to wide variations in the pH value of the physiological fluids, sol–gel conversion induced by pH changes seems to be an ideal approach for enhancement of the pharmacological efficacies of the topical drug delivery, especially ophthalmic and intravaginal applications. One of the most widely used polymers with thixotropical property is polyacrylic acid (PAA), whose aqueous solutions were less viscose and acidic in nature, and were transformed into gels upon increasing the pH [34]. PAA gels in ophthalmic application demonstrated a long retention time of about 5 h and a long duration of action mainly due to the high yield stress which governs the shearing action of eyelids and movements of the eye ball in vivo. Various modifications on PAA gels were made to enhance its efficacy as a drug delivery system. Hydroxypropyl methylcellulose (HPMC) affected the rheological properties of aqueous solutions containing PAA in a pH-dependent manner. PAA in the presence of HPMC formed a low viscosity liquid at pH 4.0 and upon increasing the pH to 7.4 transformed into stiff gels with a plastic rheological behavior and comparable viscosities, which was suitable as a liquid ophthalmic delivery system for timolol maleate [35].

Table 1
The factors affecting thixotropic property of formulations.

Factors	Polymer	Application	References
PH	PAA (polyacrylic acid), ethyl cellulose, acetophthalate latex	Sol–gel conversion from acidic pH 3.5–4.5 to neutral or alkaline pH by tear fluid or cervical fluid.	[30,34,36]
Temperature	Xyloglucan, Poloxamer 407 (pluronic derivatives)	Conversion of thermo-reversible gels between room temp and body temp (skin, eye or vagina)	[37,38,40]
Polymer concentration	Carbopol (polyacrylic acid derivative), NaCMC	An incorporation of HA (0.00–0.20%) into Carbopol gels (0.00–2.0%); NaCMC (20%) was optimal for a local delivery.	[52,54,55]
Polymer combinations	PAA, carbopol, xyloglucan,	PAA in combination with HPMC or hydroxypropyl cellulose; CMC and PVP; xyloglucan and pectin	[35,44,56,58]
Polymer modification	PAA; HEC vs. HMHEC; Diacid amides of dicholesteryl L(D)-alaninates	PAA and L-cysteine; HMHEC had better thickening ability due to the hydrophobic alkyl chains; Formation of porous columnar mesophases.	[60,61,63]
Addition of cations or anions	Gelrite solution; sodium alginate or chitosan dispersions	Sodium, calcium; MAS	[64–66]
Addition of excipients	Carbopol; Na-DOC; fluorinated liquid carrier	Lecithin, sodium chloride, potassium chloride, ammonium sulfate, carbamide, mannitol, xylitol, sorbitol and glycerol.	[68–71]

PAA (polyacrylic acid), HA (hyaluronic acid), HPMC (hydroxypropyl methylcellulose), HEC (hydroxyethylcellulose), HMHEC (hydrophobically modified hydroxyethyl cellulose), CMC (carboxymethyl cellulose), NaCMC (sodium carboxymethyl cellulose), Na-DOC (sodium deoxycholate), PVP (polyvinylpyrrolidone); MAS (magnesium aluminum silicate: a negatively charged clay).

On the contrary, some co-solvents make PAA gels become more stable against pH or temperature changes. Carbopol polymers (i.e., PAA derivatives) were prepared in a co-solvent system comprising water, propylene glycol and glycerol, and subsequently neutralizing the carboxylic groups of the polymers with triethanolamine [36]. The theological behavior of the carbopol microgels did not change appreciably in the pH range of 5.0–8.0, and the gels were used as an effective dermatological base for topical applications.

The pH dependence of thixotropy was also observed in other polymers like pluronics (i.e., a registered brand of Poloxamer (BASF Co.)), tetronics, ethylcellulose and acetophthalate latex, being coagulated upon increasing or decreasing the pH by physiological fluids including tear fluid and cervical fluid. Non-aqueous suspensions containing positively charged aluminum magnesium hydrotalcite and cationic starch showed an increase in consistence coefficient and equilibrium viscosity at the range of near neutral and basic pH, whereas they showed a decrease at the acidic pH range [30]. It is also observed that the mixture exhibited positive, negative or complex thixotropy according to pH and the mass ratio of the two compounds.

6.2. Temperature

Thermo-reversible gels can be used as a delivery system which requires a sol–gel transition at body temperature. Poloxamer-407 exhibited significantly less toxicity and non-interruption of vision as compared with other commercially available polymers, which are suitable properties for the ocular drug delivery systems [37]. Poloxamer is a block copolymer which comprises of polyoxyethylene and polyoxypropylene and forms a gel upon interacting with other chemicals, such as chondroitin 6-sulfate (C6S) [38]. The viscosity of Poloxamer increased with temperature or composition changes, and the combination with other Poloxamer derivatives, further enhancing corneal resident time due to suitable phase transition temperature [39].

Xyloglucan obtained from tamarind seeds forms a thermally reversible hydrogel [40], whose gelation time and temperature are easily altered by modifying the galactose removal ratio in the presence of enzymes like β-galactosidase [41]. The gels made of xyloglucan had a higher viscosity than those made of Poloxamer at the constant shear rates. The thixotropic morphology was in a close correlation with the temperature at which they were prepared and concentrations of the hydrogels, obtaining strong hydrogels with an open 3-dimensional network comprised of thin membranes at 3% at 37 °C. Thermally reversible xyloglucan formulations have been applied to various delivery routes including oral [42–44], rectal [45], intraperitoneal [46], ophthalmic [47,48] and percutaneous [49] administrations.

6.3. Concentrations of the polymer(s)

There is a well-established relationship between apparent viscosity and spreadability of gels [50]. The optimal concentration of the components in the formulation with the most thixotropic property needs to be defined to obtain the highest pharmacological efficacy. The Poloxamer based system developed for the ophthalmic drug delivery showed the strong concentration dependence of sol–gel–sol conversion [51]. A rheological property of binary hydroalcoholic gels made of Carbopol Ultrez 10 (U10) and hyaluronic acid (HA) varied as a function of the polymer concentration [52]. The mixture was a liquid with less viscosity, exhibiting plastic behavior and readily being transformed to stiff gels. An incorporation of HA (0.00–0.20% w/w) significantly improved the property of PAA (0.0–2.0% w/w), which has direct repercussions on the ease and efficiency of its application to the skin.

The following systems exhibited varying degrees of a thixotropic behavior according to their composition ratio. A bioadhesive formulation made of hydroxyethyl cellulose (HEC), polyvinyl pyrrolidone (PVP) and polycarbophil (PC) demonstrated that an increase in the concentration of HEC leads to the formation of dispersed solids of PVP and PC [22]. The large amount of suspended solid was the major source for the significant enhancement of hardness and viscosities of the products containing 5% w/w HEC. Micro-emulsions containing soya phosphatidylcholine (SPC), polyoxyethylen glycerol trihydroxystearate 40 (EU) and sodium oleate (SO) as oil phase and aqueous buffer were developed as a carrier for doxorubicin [53]. Pseudo-ternary phase diagrams yielded the optimal combination of SPC/EU/SO at the weight ratio of 3.5:3.5:3. The apparent viscosity increased 25- and 13-folds with the constant cholesterol concentration for drug-free and drug-load micro-emulsions, respectively.

The bioadhesive polymer system was prepared from a polyethylene gel containing various amounts of sodium carboxymethyl cellulose (NaCMC) as an adhesive and hydrolysed gelatin as a water sensitive material to ensure rapid swelling [54,55]. In vitro release profiles of a local anaesthetic drug, febuverine hydrochloride, from a hydrophobic gel containing 34% adhesive hydrocolloids demonstrated that the adhesive bond strength of the formulations was dependent on the NaCMC content, showing a maximum strength at the content of about 20%.

6.4. Polymer combinations

It was found that the proper rheological and mechanical properties were integral in the mucosal and buccal formulations and that they should exhibit a plastic or pseudo plastic flow with thixotropy, long duration of action, hardness and easy spreadability [22]. To enhance the bioadhesive strength of mucoadhesive formulations, various combinations of hydrophilic polymers like carbopol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose and polyvinyl pyrrolidone were evaluated.

The amount of PAA needed in the stiff gels was significantly reduced by the combination of HPMC. It was shown that HPMC had no interactions with PAA and acted only as a viscosity enhancing agent. An aqueous mixture of 1.5% HPMC and 0.3% PAA exhibited the rheological characteristics that were similar to those of 2.0% PAA solution [35]. The rheological study showed that the formulation containing a combination of carbopol and HPMC at the ratio of 2:1 gave the highest viscosity and exhibited apparent pseudo plastic thixotropic behavior, which was suitable as a topical gel vehicle for nystatin [56]. In another study, it was found that the optimum concentrations of Carbopol 980NF and HPMC for the in situ gel-forming systems as a viable alternative to conventional puerarin eye drop were 0.1% (w/v) and 0.4% (w/v), respectively [57].

The studies on bioadhesive polyethylene glycol gels containing varying combinations of carbopol 934P and polyvinyl pyrrolidone K90 showed that those gels were pseudo plastic in nature and exhibited enhanced thixotropy [58]. The break down of the structure in the gel assessed by the area within the hysteresis loop confirmed that the concentration of carbopol varied positively with the zero-rate viscosity. An addition of pectin, whose gelation process is ion responsive, to the xyloglucan solutions having thermally reversible gelation characteristics significantly reduced the gel erosion rate and achieved the sustained release profiles of model drugs including paracetamol [44].

6.5. Modification of polymer structure/component

Thixotropic property plays a key role in liquid filling of hard gelatin capsules, and there is a positive relationship between the dispersed phase for the proper filling of molten dispersions into capsules and apparent viscosity of the formulation [59]. A gelation test revealed that a subtle change in the length of the spacer and an inverse chirality of the amino acid residue can produce a dramatic change in the microstructures, thixotropic properties of the gels and the gelation

behavior of the compounds, such as diacid amides of dicholesteryl L(D)-alaninates [60,61].

The bulk structural characteristics of porous columnar mesophases observed from the twin-dendritic organo-gelators prepared through selective functionalization of N-(3-aminopropyl)-1,3-propanediamine (APPDA) with self-assembling dendrons using 1,1′-carbonyldiimidazole (CDI) were indicative of the subsequent gel properties [62]. It was also found that hydrophobically modified hydroxyethyl cellulose (HMHEC) showed much better thickening ability in oil-in-water emulsions than parent hydroxyethyl cellulose (HEC) from which it was derived. At higher concentrations, HMHEC forms an elastic gel, which has good thixotropic properties mainly due to the association of the hydrophobic alkyl chains which are absent in HEC [63].

6.6. Addition of cat/anions

An addition of cat/anions significantly affected the viscosity of the thixotropic formulations. Gelrite, a polysaccharide of low acetyl gellan gums, exhibited pseudo plastic behavior, and both mono and divalent gelrite form a clear gel depending on the concentration of individual cations [64]. Due to its optimal viscosity and pseudo plastic nature as well as ocular tolerance, low toxicity, withstanding sterilization conditions, the gelrite based system yielded the transition temperature of above 34 °C and was suitable for the ophthalmic drug delivery, achieving less drainage from the pre-corneal area and extended the drug residence time in the conjunctiva sac.

An incorporation of magnesium aluminum silicate (MAS), negatively charged clay, into sodium alginate (SA) or chitosan (CS) dispersions enhanced the viscosity and shifted the flow type from Newtonian to a pseudo plastic flow with thixotropic properties [65,66]. Heat treatment caused a significant decrease in viscosity and hysteresis area of the composite dispersions, suggesting that the electrostatic interaction between MAS and SA or CS induced a change in flow behavior and flocculation of the composite dispersions.

6.7. Addition of excipients

An addition of excipients, such as lecithin, sodium chloride and glycerol, to the gel system significantly affected its viscosity, producing viscous thixotropic gels with enhanced stability of the system [67]. Lecithin, a permeation enhancer, induced sol–gel conversions of Poloxamer 407 gels through the formation of micellar structures and affected in vitro permeation rate of triamcinolone acetonide, which was reversely correlated with the lecithin concentration [68]. Physicochemical characterization by rheology, melt solidification and moisture uptake revealed that an addition of 10% (w/w) lactose to poloxamers enhanced its thixotropical property and efficacy as a hard gelatin capsule [59].

An addition of surfactant (0.5–5.0% Tween 80) to the aerosol nasal sprays made of carboxymethyl cellulose (CMC) and carbopol 934 PNF solution influenced viscosity and appearance of the thixotropic system [69]. The pharmacological efficacy of nasal aerosol is significantly affected by the combined outcomes of the physicochemical properties including actuation force, viscosity, rheological properties and surface tension. It was also found that vehicles formulated in fluorinated liquid carrier containing colloidal silicon dioxide as a suspending aid were thixotropic and bacteriostatic in nature [70].

Sodium deoxycholate (Na-DOC) gels were evaluated as a drug carrier for topical and cosmetic preparations [71]. Na-DOC is a naturally occurring bile salt with a molecular weight of 414.5 kDa and has capability to form films. An addition of excipients, such as sodium chloride and glycine, to the Na-DOC system produced viscous thixotropic gels with enhanced microbial stability. Na-DOC systems also enhanced the membrane permeability of the loaded drugs, which makes them a reliable vehicle for topical and cosmetic preparations.

7. Pharmaceutical applications of thixotropy

The time-dependent change in viscous nature of thixotropy finds its major applications in pharmaceutical formulations including hydrogel, ointment, suspensions and emulsions through various routes including oral, topical, ophthalmic and mucosal administration, as shown in Table 2.

7.1. Thixotropy in controlled drug release

Thixotropical property plays an integral role in defining therapeutic efficacy of the pharmaceutical formulations by contributing their extended retention time at the administered site and enhanced systemic bioavailability. A non-Newtonian behavior of the thixotropic sol–gel system is expressed with yield values which are required to break down the solid structure and to initiate plastic flow. Yield value and plastic viscosity are material properties, whereas the thixotropy mainly depends on the shear history of the material and the degree of dispersion. An increase of the yield value indicates a gradual strengthening of the three-dimensional network structure of thixotropic formulations.

In the drug delivery systems, the modification of the rheological properties appeared to influence the controlled release of loaded drugs from the topical formulations, and achieved by mixing gelating or emulsion components which form a highly interconnected network within the system [72]. Bioplastics made of glycerol and wheat gluten showed a high capability for thermosetting modification and their hygroscopic properties depend on plasticizer nature and processing procedure [73]. The high water absorption and controlled release profiles of the target compound, KCl, from bioplastic samples were obtained by modulating thixotropical property of a given formulation through an addition of plasticizers at selected processing conditions.

The components of body fluids, which are principally water, serve as a major factor in controlling the yield value and subsequently

Table 2
The pharmaceutical application of thixotropic property.

Application site	Formulation types	Polymers/components	References
Ophthalmic	Sol–gel formulation; nanoparticles	PAA; gelrite solution	[34,51,57,78,79]
Vaginal	Sol–gel formulation	Carbopol; HPMC based gel	[54,61,83]
Parenteral	Suspension; hydrogel	Sodium citrate and polysorbate 80; triblock copolymer and alpha-cyclodextrin (alpha-CD)	[85–87]
Topical hydrogel	Semi-solid hydrogel	PAA; carbopol; sodium alginate	[89,91]
Other topical	Ointment; micro-emulsion; aqueous suspension	A mixture of oil and water; carrageenan based micro-emulsion gel	[93,94]
Sunscreens	Lotion; film	Phosphate-based SEB+ PVP/eicosene (PVP/EC)); a mixture of ZnO/TiO_2	[96–98]
Nasal	Spray suspension	Aqueous suspension with the excipients; phosphoinositide 3-kinas	[100–102]
Dental	Gel, gelatin microparticles	Polyethylene gel containing NaCMC; propolis mixed with surfactant, isopropyl myristate and water	[56,103–107]

PAA (polyacrylic acid), HA (hyaluronic acid), HPMC (hydroxypropyl methylcellulose), NaCMC (sodium carboxymethyl cellulose), PVP (polyvinyl pyrrolidone), SEB (self-emulsifying bases).

system structures with thixotropical property. Body fluids can diffuse into the solid matrices of sol–gel system, whose structure, especially the number of cross links formed and the hydration level, was affected by fluid components, and so the release rate of the encapsulated drugs. In an oral application of thixotropic formulations, a constant flow of simulated saliva solution (4 ml/min) affected the drug-release rate from gel samples; PEG gel (a Newtonian formulation) base dissolved gradually upon exposure to simulated saliva, while a gel base containing a mixture of Carbopol and polyvinyl-phenol (a non-Newtonian formulation) swelled and formed a viscous barrier to drug release, requiring different times to achieve complete release of loaded drugs from each system [74].

In another study, Guar gum (GG) based hydrogel was developed as an injectable hydrogel drug delivery system with thixotropic property [75]. The GG hydrogel showed a maximum water uptake at acidic (pH 1) and basic (pH 10) values. It was suggested that at acid pH, most OH groups were protonated and the polymer chains were kept away by the electrostatic repulsions among the positively charged groups which are very hydrophilic and hence allow the entrance of water inside the gel structure. At basic pH, most of the OH groups were deprotonated and induced an electrostatic repulsion between the negative charges along the polymer chains and thus the entrance of the water was promoted for the same reason [75]. It was also found that the release rate of metronidazole (MZ), a common antibacterial drug, from GG hydrogel was subject to pH and diffusion rate of a fluid flow.

The results of these studies supported that modification of the gelation process by the components of physiological fluids have a direct impact on the controlled release rate of loaded drugs from the thixotropic formulations.

7.2. Ophthalmic formulations

The conventional ocular drug delivery systems like solutions, suspensions and ointments showed drawbacks, such as increased pre-corneal elimination, high variability in efficiency and blurred vision. Various formulations including gels [35] and nanoparticles [76] with thixotropic property have been developed as an ophthalmic drug delivery system to address these drawbacks.

The properties suitable for ophthalmic delivery systems provide a response to environmental changes, such that the liquid formulation upon instillation undergoes phase transition in the ocular cul-de-sac to form a viscoelastic gel. It was reported that aqueous PAA gels administered into rabbit eyes could be retained for 4–6 h and resulted in a longer duration and greater activity of incorporated pilocarpine compared with viscous drug solutions [34,77]. The long retention time of the viscous gels is attributable to their high yield stress values, which allow them to withstand in vivo shearing action of eyelid and eyeball movements. Another attempt to enhance the ophthalmic efficacy of timolol maleate loaded in PAA gels was successfully carried out by accommodating buffering action from tear fluids through the addition of inert polymers, such as hydroxypropyl methylcellulose (HPMC) [35].

The environmentally responsive gel formulation was developed to improve ocular bioavailability of carteolol hydrochloride (HCl) and hence decrease its systemic absorption and side effects [78]. Gelrite formulation (0.4% w/w) made of polysaccharide low acetyl gellan gum and containing 1% drug showed significantly improved bioavailability as compared with the commercial aqueous solution (Arteoptic 1%) [64]. Gelrite formulations with pseudo plastic behavior seemed to be suitable for the ophthalmic delivery of timolol maleate, an alkaline anti-glaucoma drug, achieving long residence time in the conjunctiva sac [79]. The efficient ophthalmic application of the formulation with thixotropical property warranted continuous investigation on the feasibility of the similar formulation to other topical treatment.

7.3. Vaginal formulations

The vaginal drug delivery route has been widely used for topical delivery of microbicides or hormones [80]. The major challenge in vaginal drug delivery is the limited contact time due to various protective mechanisms of the vagina thereby leading to short duration of action and less therapeutic efficacy. To remain in the cervics, the formulation must be thick enough not to run out of the vagina or flow down the back of cervics.

Rheological behavior of vaginal gels is often dependent on the type of gelling agent used, which directly influences their spreading and retention properties upon application. The reversible thixotropic property of polymer allows solutions to flow onto the cervical cavity permitting an intimate surface contact before it forms a non-occlusive gel upon pH change [81]. Since gelation is reversible, removal is facilitated by immersion in or turning back to the original pH. An increase in viscosity leads to a prolongation of system's contact time on the delivery site [54] and further fulfills their therapeutic purposes.

Mucoadhesive polymers, such as polycarbophil, carbopol, hydroxylpropyl cellulose and PVP, were tested as in situ gelling systems to enhance the adhesiveness of drug onto the surface of the vaginal mucosa [82]. The sol–gel thixotropic formulation developed for intravaginal delivery of microbicidal agents against sexual transmitted diseases exhibited acceptable mechanical characteristics, such as ease of application, low hardness and an extended retention period at the site of application [83]. The flow properties of intravaginal formulations and their rheological characteristics were controlled by pH, in which the initial exposure of the formulation to acidic pH (i.e., normal healthy vagina pH 4.5) is affected by neutral pH of male partner's serum, subsequently extending its resident time at the vaginal cavity and enhancing microbicidal efficacy.

Further modifications on the conventional mucoadhesive formulations have been made to gain a prolonged residence time and a sustained drug release in the vagina. L-Cysteine and cysteamine, respectively, were covalently attached to PAA to design a novel vaginal delivery system [61]. These thiolated polymers had an enhanced thixotropical property and provided a prolonged and sustained release profile of nystatin under physiological conditions.

7.4. Parenteral formulations

It is of strong interest for biomedical field to develop a hydrogel which is able to pass through a needle without losing its structure. An ideal thixotropic liquid should have high consistency under the storage conditions yet being removed easily. It should not settle in the container, convert to the fluid on shaking and rapidly regain its consistency to keep particles in the suspended state. In case of suspensions, it is observed that the rate of settling of particles is slowed with an increase in thixotropy, which is a useful phenomenon for stabilization and efficacy enhancement of the parenteral pharmaceuticals.

The formation of cohesive and compact deposits at the injection site can be attributed to a major source for the prolonged therapeutic action of parenterals [84]. The concentrated parental suspension (40–70%) of procaine penicillin G, which was mixed with the small amounts of sodium citrate and polysorbate 80 in water, was decomposed as it passes through the hypodermic needle [85]. The consistency was regained upon rebuilding of the structure which led to the formation of drug depot in the body. The low water solubility and tendency to form cohesive deposits retarded the release rate of penicillin G.

A new class of bioabsorbable supramolecular hydrogels formed through self-assembly between biodegradable poly(ethylene oxide)-poly[®-3-hydroxybutyrate]-poly(ethylene oxide) (PEO-PHB-PEO) and alpha-cyclodextrin (alpha-CD) was developed as a novel injectable system [86,87]. The gelation kinetics after injection was

dependent on the concentrations of the polymer and alpha-CD as well as the molecular weight of PEO used. The thixotropic and reversible hydrogel formation is based on physical cross-linking induced by supramolecular self-assembling, which voluntarily occurred even in the absence of any chemical cross-linking reagents.

In another study, 50% hydrogels made of hyaluronane and alginate were synthesized, their thixotrophic behavior was verified, and their mechanical properties were determined before and after the passage through the needle [88]. The unique property of these gels to flow like a liquid with thixotropic behavior allowed them to be used as an injectable hydrogel drug delivery system for various bioactive agents (drugs, proteins, vaccines or plasmid DNAs). The thixotrophic property of these hydrogels was applied to a cell-containing material that supports cell proliferation and growth permitting in vivo engineering of new tissues, retaining cell suspension entrapped inside the hydrogel structure and achieving enhanced cell growth. Recently, Guar gum (GG) based hydrogel showed a similar but more controllable characteristics to previous hydrogel formulations in an application to metronidazole (MZ), a common antibacterial drug, which was subject to pH and diffusion rate of a fluid flow [75].

7.5. Topical hydrogel formulations

To overcome the problems associated with other dosage forms, non-aqueous, thixotropic vehicles are formulated in various polymers along with suspending aids which ensure uniform distribution and prolonged action of the incorporated drug or polymeric material on the topical sites. Due to the high mucoadhesive properties and the strong in situ gelling properties of polyacrylic acid (PAA) polymers, hydrogels prepared with macromolecules seem to be a promising vehicle for imidazole-loaded lipid nanoparticles, such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Semi-solid formulations based on SLN and NLC prepared using Carbopol 934 had pseudo plastic behavior with thixotropic properties and demonstrated its usefulness as topical particulate carriers for imidazole antifungal agents [89].

An amidic derivative of a carboxymethylcellulose-based hydrogel formed a homogenous three-dimensional scaffold, which maintained the thixotropic property of the linear polysaccharide [90]. Amphiphilic derivatives of sodium alginate, prepared by chemical covalent binding of long alkyl chains onto the polysaccharide backbone via ester functions, form strong hydrogels in aqueous solutions with shear-thinning and thixotropic behavior [91]. This hydrogel was used for the encapsulation of model proteins, such as bovine serum albumin (BSA), human hemoglobin (Hb) or a vaccine protein (Helicobacter pylori (H. pylori) urease).

7.6. Other topical formulations

Various thickening agents have been used to obtain proper viscosity of the topical products like ointment, emulsion and aqueous suspension, converting the flow properties from Newtonian to thixotropic (i.e., non-Newtonian) at the application sites. It was found that vehicles made of non-ionic macromolecular surface active compounds, polyoxyethylene fatty acid from Rokacets group, were non-Newtonian systems, viscoelastic and highly thixotropic [92]. The types of morphine salt affected the spread and viscosity of transdermal absorption of morphine sulphate from the emulsion ointment based on polyoxyethylene fatty acid, revealing that formulations with morphine hydrochloride yielded more alkaline pH and had less viscoscious.

Due to the potential to act as a drug delivery system for vitamins, micro-emulsions have been widely used in the pharmaceutical field. The micro-emulsions containing an isotropic mixture of oil and water, and prepared using the homogenization process are thermodynamically stable. The dermal delivery of vitamins C and E in the micro-emulsion, o/w, w/o type, achieved better vitamin stability as compared with the conventional formulations including aqueous/non-aqueous solutions. Among all the formulations, gel like o/w micro-emulsion provided most protection to both vitamins C and E [93]. The changes in internal organization of micro-emulsions induced by the addition of a thickener were the most influential factor that determined the stability of vitamins in thickened systems.

The micro-emulsions made of various polymers were also thixotropic. A micro-emulsion based gel made of the suitable polymers, such as carrageenan, became a shear-thinning system and enhanced the topical efficacy of flurbiprofen due to the long exposure time of the loaded drug from the cohesive deposits [94].

7.7. Sunscreen formulations

Sunscreen formulations are one of the rapidly growing products in the pharmaceutical markets. Sunscreen formulations must exhibit pseudo plastic behavior, so that they produce a coherent protective film over the skin surface [95]. However, most Newtonian systems fail to form a protective film over the skin, since they spread on the skin very rapidly. Film thickness, opacity and uniformity of the sunscreens are the required properties to be optimally regulated during the formulation process. The stability of the products should also be fully taken into account, since the cosmetic formulations currently in the market contain enzymes and vitamins that have an anti-oxidant property.

Sun protection factor (SPF) is a major criterion in the selection of the sunscreen formulation [96]. The distribution of the UV filters uniformly on the surface led to a higher SPF value. In relating thixotropy to SPF, the compounds with the low thixotropy values had a statistically higher SPF. Poor spreadability and uneven distribution of the sunscreen is observed with the thixotropy values lower than the optimal values and on the other hand an uneven film is resulted with the thixotropy values of higher than optimum. Therefore, it is integral to find the optimum thixotropy value for the sunscreen formulations.

The physical stability of sunscreens made of phosphate-based self-emulsifying bases (SEB) and polyvinyl pyrrolidone/eicosene cross-polymer (PVP/EC) showed high thixotropy, which subsequently demonstrated a high SPF and stability [97]. An addition of metal oxides based on sodium lauryl sulphate/polysorbate 80, triethanolamine stearate, and cetyl trimethyl ammonium chloride to a 1:1 mixture of ZnO/TiO_2 (zinc oxide and ultrafine titanium dioxide) prepared as 5% dispersions in sunscreen formula significantly influenced the magnitude of viscosity [98]. The cationic emulsion base was found to be the most stable to incorporate the microfine metal oxides in sunscreen formula.

7.8. Nasal formulations

The major limiting factor for drug delivery to the nasal mucosa has been the mucociliary clearance. It was reported that thixotropic solutions containing methylcellulose derivatives lowered the clearance rate and enhanced the bioavailability of the drugs administered through the nose by immobilizing the virus on the airway epithelia [99].

The rheological profiles of commercial corticosteroid nasal spray suspensions made of phosphoinositide 3-kinase demonstrated that they were shear-thinning and thixotropic to varying degrees [100]. The rheological properties of corticosteroid nasal sprays containing triamcinolone acetonide or mometasone furonate showed time-dependent, reversible loss of viscosity under shear (e.g., shaking or spraying), indicating that when initially shaken and dispensed, they flowed more freely, followed by recovery of viscosity that would likely inhibit the suspensions from flowing out of the nasal cavity [101–102]. The high viscosity present in most commercially available sprays even after structure breakdown is the controlling factor for prolonged residence of the spray in the nasal cavity.

7.9. Dental formulations

Formulations with the thixotropic property can be applicable to the treatment of periodontal diseases like gingivitis and periodontitis, in which inflammation and plaque formation in the deeper tissues produce a space or pocket between the roots. The bioadhesive polymer system prepared from the polyethylene gel containing various amounts of sodium carboxymethyl cellulose (NaCMC) as an adhesive, and hydrolysed gelatin as a water sensitive material was thixotropic and effective in an oral delivery of local anaesthetic agents, such as febuverine hydrochloride [56].

The gelatin microparticles containing propolis, which has shown anti-microbial, anti-inflammatory and anti-oxidant activities [103], in combinations with surfactant, isopropyl myristate and water were pseudo plastic and thixotropic in nature, which was used as an efficient drug delivery system for the treatment of periodontal diseases [103,104]. The rheological tests on two low viscosity vinyl polysiloxane (VPS) impression materials assessed by Dynamic Stress Rheometer featured with cone and plate geometry elucidated that VPS was thixotropic with a yield stress of around 40 Pa and had non-drip properties which prevent them from flowing off an impression tray during insertion of the material into the mouth [105].

A thixotropic pluronic gel (20% wt./wt.) was developed for periodontal delivery of tetracycline [106]. Colloidal silicon dioxide (Aerosil 200) is a gelling agent that causes significant changes in the liquid crystalline phases and modifies the rheological properties. The in vivo study performed to evaluate the clinical efficiency of the liquid crystalline gel showed that an addition of Aerosil to the gel favored hexagonal phase formation. Viscosity and bioadhesivity increased with an increase in the concentration of Aerosil and the release rate of tetracycline was sustained as the concentration of Aerosil increased. Various clinical parameters confirmed the acceptability and efficiency of this gel system for tetracycline delivery.

The study on the rheological behavior of calcium alginate impression materials revealed that the gelation time is primarily controlled by the concentration of $Na_4P_2O_7$ in solution acting as a retarder, whereas the level and particle size of the alginate and $CaSO_4 \cdot 2H_2O$ affected the kinetics through the dissolution rates and concentration effects [107]. Calcium alginate impression materials have been used as dental impression pastes due to the limitations of existing materials and the very exacting conditions of the oral environment. The results of these studies have demonstrated the usefulness of propolis, VPS and calcium alginate impression in dental application.

8. Conclusion

The application of thixotropic properties to the pharmaceutical formulation has become an enormously challenging task in the past few years. The complex thixotropy observed in suspensions, emulsions and hydrogel, in which an early positive thixotropic property is replaced with negative thixotropic property upon changes in pH or temperature, is an ideal phenomenon for novel pharmaceutical formulations. The regulation of thixotropy by the addition of excipients, ions or other polymers promises to yield new insight into broad pharmaceutical applications of the rheological properties in the controlled and sustained drug delivery. This review confirms therapeutic potential of the thixotropic formulations as pharmaceutically significant platforms.

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