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Rheological studies on solid lipid nanoparticle based carbopol gels of aceclofenac

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ABSTRACT

Solid lipid nanoparticles (SLN) of aceclofenac were prepared using Taguchi experimental design by Trotta method. The prepared SLN were formulated into a gel preparation, using carbopol 940. Gels were evaluated for drug content, bioadhesion and their stability against change of temperature and shear. The viscosity of prepared gels was found to be temperature independent. Rheological behavior of gels with changing shear was rather complex. Viscosity varied inversely with shear but remained almost constant during short spans of time when shear was kept constant. Viscosity of the gels did not change if shear was not varied. *In vitro* diffusion studies exhibited an immediate release followed by a sustained release. This could help in maintaining the concentration of bioactives such as aceclofenac in desirable levels at sites of inflammation and injury.

1. Introduction

Solid lipid nanoparticles (SLN) are particles of submicron size (50–1000 nm) stabilized by a surfactant and made from lipids that remain in a solid state at room/body temperature. SLN have emerged as alternative carriers to colloidal systems, for controlled and targeted delivery. They are made up of biocompatible and biodegradable material, capable of incorporating lipophilic and hydrophilic drugs [1–3]. Gels of pharmaceutical significance have been prepared by using various types of materials. Carbopol is one such commonly used polymer of acrylic acid which can be crosslinked either with polyalkenyl ethers or divinyl glycol. Gels can be produced from primary polymer particles of about 0.2–6.0 μm average diameter. The flocculated agglomerates cannot be broken into the ultimate particles when converted in to gel form. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking [4].

Carbopols readily absorb water, get hydrated and swell. Different grades of carbopol polymers exhibit different rheological properties depending on their particle size, molecular weight between crosslinks (M_c), distributions of M_c and fraction of the total units which appear as terminal, i.e. free chain ends. The M_c for carbopol 940 has been reported as 1450 monomer units (or $1450 \times 72 = 104{,}400$ g/mole) [5]. Carbopols are essentially nontoxic and nonirritant materials with no evidence of their hypersensitivity in human subjects when used topically [6].

Viscoelasticity is a mechanical property of materials that possess a combined behavior of elastic solid and viscous fluids. These materials include melt polymers, food and pharmaceutical semisolid dosage forms such as cream, ointment and gels [7]. Viscoelastic properties of pharmaceutical gels affect their physical appearance, patient or consumer perceptions, their spreadability and flow behavior [8]. Various researchers have tried to explore the rheological properties of carbopol gels through continuous shear [9–11]. This can deform the gel structure and data thus obtained does not really represent the intact gel structure. Rapid visco analyzer (RVA) is a controlled shear rate instrument through which a constant shear rate (rpm) can be applied and the resultant torque (force, shear stress) measured. Torque and displacement are converted to rheological format by means of measuring system constants. Data can be produced in both tabular and graphical format. RVA is a Searle type viscometer, with a stationary bowl and a combined stirring and sensing element suspended concentrically. Nonlaminar or turbulent flow at high speeds prohibits absolute viscosity measurements, an effect which is exacerbated by the mixing-paddle design of the sensor element [12]. In the current work, carbopol gels of aceclofenac loaded SLN dispersion were prepared and analyzed using RVA at both constant shear and temperature with changing rate of shear, in an attempt to obtain a better picture of the rheological behavior of intact gels. Although RVA has been used frequently in food industry [12,13], this study reports for the first time its use in pharmaceutical gels.

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Table 1
Real and orthogonal values of L9 design and resulting characterization parameters.

Batch	Independent variables				Characterization parameters		
	Type of lipid [*A*]	Drug:lipid ratio [*B*]	Surfactant conc. (%) [*C*]	Sonication time (min) [*D*]	PS (nm)	ZP (mV)	PI
1-B	CA (1)	1:5 (1)	1.5 (1)	2 (1)	191.2 ± 5.93	−10.70 ± 0.18	1.000 ± 0.001
2-B	CA (1)	1:7 (2)	2.0 (2)	5 (2)	161.8 ± 4.92	−8.17 ± 0.19	0.753 ± 0.007
3-B	CA (1)	1:10 (3)	2.5 (3)	8 (3)	146.7 ± 8.95	−10.00 ± 0.50	0.956 ± 0.012
4-B	GP (2)	1:5 (1)	2.0 (2)	8 (3)	56.8 ± 0.87	−11.00 ± 0.18	0.949 ± 0.009
5-B	GP (2)	1:7 (2)	2.5 (3)	2 (1)	69.3 ± 2.97	−11.40 ± 0.23	0.600 ± 0.034
6-B	GP (2)	1:10 (3)	1.5 (1)	5 (2)	49.5 ± 1.30	12.30 ± 0.14	0.450 ± 0.009
7-B	GB (3)	1:5 (1)	2.5 (3)	5 (2)	149.2 ± 8.96	−5.42 ± 0.05	0.852 ± 0.009
8-B	GB (3)	1:7 (2)	1.5 (1)	8 (3)	245.0 ± 12.61	−6.75 ± 0.03	0.761 ± 0.011
9-B	GB (3)	1:10 (3)	2.0 (2)	2 (1)	123.6 ± 9.47	−8.10 ± 0.08	0.580 ± 0.010

Figures in parentheses indicate the levels of different variables: 1 = low, 2 = medium, and 3 = high; CA = cetyl alcohol, GP = precirol, GB = compritol, PS = average particle size, ZP = zeta potential, and PI = polydispersity.

2. Materials and methods

2.1. Materials

The drug, aceclofenac, was procured as gift sample from Arbro Pharmaceuticals, India. Carbopol 940, Cetyl alcohol (CA) and triethanolamine were procured from SD Fine Chemicals, India. Compritol or glyceryl behenate (GB) and precirol or glyceryl palmitostearate (GP) were obtained as gift samples from Colorcon Asia Pvt. Ltd., India. The surfactant, poloxamer 188 (Lutrol F 68) was received *ex-gratia* from BASF, Germany.

2.2. Experimental design

The batches were prepared as per Taguchi experimental design. The L9 orthogonal array was used (Table 1). Orthogonal array is a matrix of numbers arranged in columns and rows. The Taguchi method employs a generic signal to noise (S/N) ratio to quantify variations. These ratios are meant to be used as measures of the effect of noise factors on performance characteristics. S/N ratios take into account both amount of variability in response data and closeness of average response to the target. There are several S/N ratios available depending upon the type of characteristics: smaller the better, as is the case with particle size and polydispersity index (PI); larger the better, as is the case with drug content and zeta potential magnitude. In some cases, a nominal S/N ratio is the best [14].

2.3. Preparation of SLN

Before preparation, the drug, surfactants and solid lipids (CA, GB and GP) were subjected to physical and spectral characterization. An absorption maximum of the drug was determined using Shimadzu Double beam UV 1700 spectrophotometer. Standard curve of the drug was prepared in methanol at concentrations varying from 10 to 100 μg/ml.

SLN were prepared by Trotta Diffusion method [15]. The lipids were used in ratios (1:5/1:7/1:10) selected by Taguchi design (Table 1). The lipids were dissolved in a mixture of minimum quantities of chloroform and dichloromethane (2 ml each). Drug was dissolved in this mixture. The aqueous phase containing surfactant was transferred to a homogenizer and lipid phase was dispersed drop by drop into the aqueous phase with a homogenization speed of 3000 rpm. After homogenization for 30 min, the resultant emulsion was poured into ice-cold distilled water up to a volume of 50 ml and stirred (2000 rpm) for 3 h to diffuse the organic solvent into external aqueous phase. It was then centrifuged at 12,000 rpm in a refrigerated centrifuge (Sartorius F18K) at 20 °C for 15 min. The solid mass, thus obtained, was dispersed in distilled water to obtain SLN dispersion. Dispersion was subjected to ultrasonication (Sartorius Labsonic P Ultrasonicator) for 2–8 min and further evaporation under reduced pressure, in a rota evaporator (Buchi), to remove traces of residual organic solvents. When tested, the resultant dispersion was found to be free from organic solvent residues.

2.4. Gels enriched with nanoparticles

Gels were prepared using carbopol 940 (1%). For the preparation of gels, glycerol (10%), nanoparticulate dispersion (20%) and distilled water were weighed in a beaker and stirred. Required quantity of gelling agent was dispersed in aqueous phase under continuous stirring. Neutralization was performed using triethanolamine to attain pH 7.0. The gels were stored in air tight amber colored glass jars.

2.5. Evaluation of SLN dispersion and gel

2.5.1. Characterization of SLN dispersion

The prepared batches of SLN dispersion were characterized on the basis of particle size, zeta potential and PI. The particle size, zeta potential and PI were measured using Malvern zetasizer (Nano ZS). Hydrodynamic diameters of particles were recorded. Each sample was made to run five times. The reported values are averages of five determinations.

2.5.2. Characterization of prepared gels

The prepared gels were evaluated for drug content, bioadhesion and their stability against change of temperature and shear.

2.5.2.1. Determination of drug content in gels. Weighed quantity of gels (10 mg) was digested with 10 ml of methanol using a vortex mixer and subsequently filtered through a Whatman filter paper. 1 ml of the filtrate was diluted with 4 ml of methanol, filtered and absorbance measured at 275 nm. Amount of drug was calculated taking into account dilution factor, if any, with the help of equation $y = 0.0048x + 0.0016$. A comparative account of drug content among different gels is shown in Fig. 2.

2.5.2.2. Bioadhesion studies on gels. The prepared gel batches were tested for bioadhesion potential. Texture analyzer equipment (TA-XT2, Stable Micro Systems, England) was used for this purpose. Gel sample was spread as a thin film on the double adhesive tape which was cut as per shape of texture analyzer probe. The probe was lowered on to a platform after selecting suitable test parameters (pre and post speed 2 mm/s; time 5 s) in the software. The force was measured and recorded as an average of three findings in Table 3.

2.5.2.3. Samples testing on RVA. Samples of gel were tested on RVA (Peten Instruments, Australia) for their stability against change of