ORIGINAL ARTICLE

To study the effect of solvent, viscosity, and temperature on the mouth-dissolving film of *Withania somnifera* Linn

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An oral-dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules, and so on. *Withania somnifera* has been used to promote health and longevity by augmenting defenses against disease, arresting the aging process, revitalizing the body in debilitated conditions, and thus creating a sense of well-being. Commercially, it is available either in powder or liquid dosage forms that do not offer patient compliance. In the present study, an attempt has been made to formulate *W. somnifera* into thin oral films. An attempt was also made to study factors like the effect of the type of solvent used for casting of the film, effect of drying temperature, and viscosity of the solution on the mouth-dissolving film of *W. somnifera* Linn. The mouth-dissolving films were prepared by the solvent-casting method. Prepared films were evaluated for film-forming capacity, appearance of film, tack test, thickness, *in vitro* disintegration time, folding endurance, tensile strength, and percentage elongation. This study illustrated that selected process variables have an influence on the physicomechanical properties of the mouth-dissolving film of *W. somnifera* Linn. Water was found to be an excellent solvent for casting when hydroxypropylmethylcellulose was used as a film former. When mouth-dissolving film of *W. somnifera* Linn was dried at lower temperatures, it showed optimum physicomechanical performances. Viscosity of the solution plays an important role in physicomechanical properties of the film; as the viscosity of solution increases, there is an increase in folding endurance, tensile strength, and percentage elongation.

Key words: *Drying temperature, nature of solvent, process variables, viscosity of solvent, Withania somnifera Linn*

INTRODUCTION

Herbal medicine is the oldest form of health care known to mankind. Herbs have been used by all cultures throughout history. They have been an integral part in the development of the modern civilization. Many drugs commonly used today are of herbal origin. Indeed, about 25% of the prescription drugs dispensed in the United States contain at least one active ingredient derived from plant material. The World Health organization (WHO) reports that 80% of the world's population relies on drugs of natural origin. Less toxicity, better therapeutic effect, and cost effectiveness are the reasons for choosing drugs of natural origin. But all the formulations of these compounds are either available in liquid forms like *arishtas* and *asavs* or the solid forms like powders that have poor palatability and hence poor patient compliance. There is a need to formulate these compounds into novel drug delivery systems so that the therapeutic effectiveness of these compounds can be clubbed with the novel advantages of these delivery systems.

W. somnifera (WS), also known as Ashwagandha, Indian ginseng, or winter cherry, has been an important herb in the Ayurvedic and indigenous medical systems for over 3,000 years. The roots of the plant are categorized as *Rasayanas*, and are described to promote health and longevity by augmenting defenses against disease, arresting the aging process, revitalizing the body in

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debilitated conditions, and thus creating a sense of wellbeing.[1] *W. somnifera* contains alkaloids (withanine, withasomnin) and steroidal lactones and glycosides also called as withanoloids and sitoindosides, and the extract of *W. somnifera* has analgesic, mildly sedative, anti-inflammatory, and anabolic activities,[2] and it is useful in stress, strain, fatigue, pain, skin diseases, diabetes, gastrointestinal disease, rheumatoid arthritis, and epilepsy,[3] chronic fatigue syndrome,[4] and even during pregnancy without any side effects.[5] It is also used as a general tonic to increase energy and improve health and longevity.[6] Clinical studies of *W. somnifera* suggest that it may promote growth in children, and improve hemoglobin level, red blood cell count, and physical performance in adults.[7]

The mouth-dissolving film belongs to novel drug delivery systems that offer unique advantages like better patient compliance, lesser excipient load, and faster onset of action. These films can be prepared either by hot melt extrusion method or solvent-casting technique. In this study, the solvent-casting method was used.

The main objective of the present research work was to study three process variables, namely, nature of the solvent used for casting of the films, effect of drying temperature, and viscosity of the solution [Figure 1]. These process parameters may affect physicomechanical properties of films. The effects of these parameters were studied on film-forming capacity, appearance of film, tack test, thickness, *in vitro* disintegration time, folding endurance, tensile strength, and percentage elongation.

MATERIALS AND METHODS

Materials

W. somnifera Linn extract was obtained from Unijules Life Science Limited, Nagpur, India. Hydroxypropylmethylcellulose (HPMC) 5 cps (cps: centipoise) (Shin-Etsu Chemical Co. Ltd, China), polyethylene glycol (PEG) 6000 (IBIS Chemie International, Mumbai), polysorbate 80 (Vinamax organics Pvt. Ltd., Mumbai), bronopol (A. B. ENTERPRISES, Mumbai), and aspartame (Aarti Pharma, Mumbai) were used as film base materials. All other chemicals and reagents were of analytical grades. Deionized double-distilled water was used throughout the study.

Methods

The effect of the nature of the solvent on the physicochemical properties of mouth-dissolving films of *W. somnifera* Linn was studied using two solvents and their combinations. The formulations were prepared according to the formula given in Table 1. The detail film forming process including variables studies was explained in the Schematic diagram as shown in Figure 1. The best formulation was selected to study the effect of viscosity of the casting solution on the properties of the film. These formulations were prepared according to the formula given in Table 2. The formulation showing desirable properties was selected for studying the effect of drying temperature on the physicomechanical properties of films. The experiment was carried out according to the conditions given in Table 3.

Table 1: Composition to study the effect of the solvent on mouth-dissolving films of *Withania somnifera* Linn

Ingredients	Percent composition				
	F1	F2	F3	F4	F5
Withania somnifera Linn extract	4	4	4	4	4
HPMC 5cps	15	15	15	15	15
PEG 6000	3.6	3.6	3.6	3.6	3.6
Polysorbate 80	1.2	1.2	1.2	1.2	1.2
Bronopol	0.01	0.01	0.01	0.01	0.01
Aspartame	1.2	1.2	1.2	1.2	1.2
Distilled water	75	–	–	–	–
Isopropyl alcohol	–	75	–	–	–
Distilled water: Isopropyl alcohol	–	–	25: 50	–	–
Distilled water: Isopropyl alcohol	–	–	–	37.5: 37.5	–
Distilled water: Isopropyl alcohol	–	–	–	–	50: 25

PEG: Polyethylene glycol, HPMC: Hydroxypropylmethylcellulose

Table 2: To study the effect of viscosity on mouth-dissolving films of *Withania somnifera* Linn

Formulation code	Viscosities of solution (in cps)
F1a	6500–7000
F1b	8500–9000
F1c	10500–11000
F1d	12000–12500

Table 3: To study the effect of drying temperature on mouth-dissolving films of *Withania somnifera* Linn

Formulation code	Drying temperature (°C)
F1bi	60–65
F1bii	80–85
F1biii	100–105
F1biv	120–125

Evaluation methods

Preliminary characteristics

Film-forming capacity: It is the ability of a polymer to form films that can be separated from the surface on which they are cast. The films were characterized as very poor, poor, average, good, better, and best depending upon their ability to form films.

Appearance of films: Appearance of film was evaluated by visual observation. The films were characterized as smooth or rough.

Tack test: Upon stacking, the films should not stick to each other. This is a criterion which a film should possess for better dispensing of dosage form.[6,7]

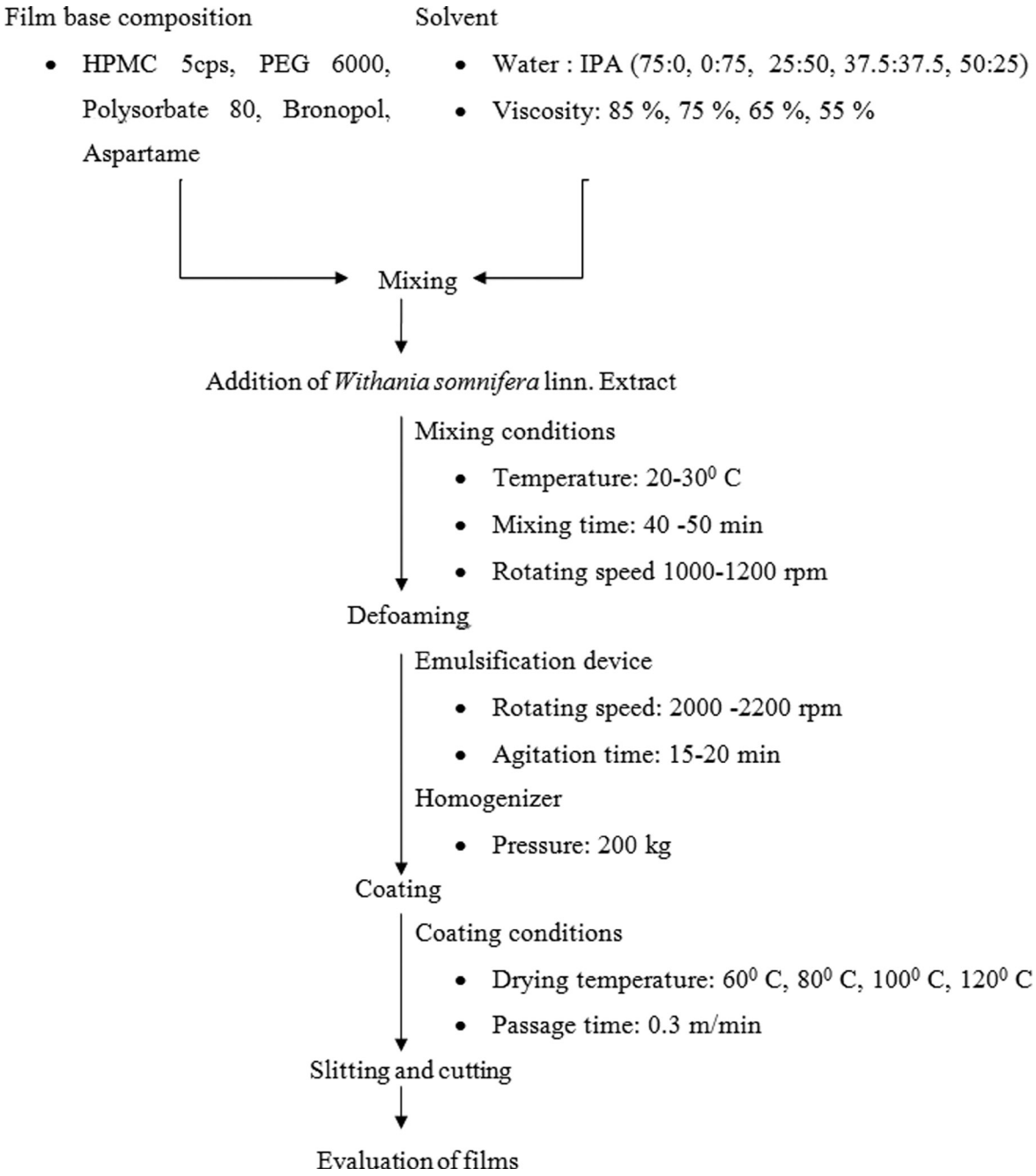

Figure 1: Schematic diagram showing film-forming process including variable studies (solvent-casting method); evaluation of films

Thickness

All the formulations were evaluated for uniformity in thickness by using calibrated digital electronic digital micrometer (IP65, Mitutoyo Co., Japan). Ten films (pieces) were taken randomly from each formulation from different places of the plate. Thickness was measured and mean value was calculated.[8]

In vitro disintegration test

Disintegration test was performed in the united state pharmacopoeia (USP) disintegration apparatus (Electrolab, Mumbai). Simulated salivary fluid (pH 6.8) was used as the medium. The films were placed in the tubes of the container and the discs were placed over it. The average *in vitro* disintegration time of six films from each formulation was noted.[9]

Folding endurance

Folding endurance was measured manually for the prepared films. A film was cut and firmly folded through the middle. The number of folds on the same crease required to produce a crack in the film was noted as the value of folding endurance.[10]

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the

applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{\text{load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}} \quad (1)$$

Percent elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of the strip divided by the original dimension of the sample. Percentage elongation was calculated by the equation as given in the equation below:[11]

$$\text{Percentage elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}} \quad (2)$$

RESULTS AND DISCUSSION

Determination of film-forming capacity, visual appearance, and tackiness for all the formulations are shown in Table 4. From the physical appearance of the film it was noted that all formulations showed rough appearance except the formulation F1, which appeared to be smooth and translucent. The formulation F1 was also found to be thin and flexible. It was observed that isopropyl alcohol (IPA) alone and in combination with distilled water exhibited poor film-forming capacity and rough surface. HPMC 5 cps is otherwise a good film-forming agent but the film-forming ability of formulations F2, F3, F4, and F5 was found to be poor; this might be because of the insolubility of HPMC 5 cps in IPA. All the films were found to be nontacky to each other.

The thickness of the formulations varied from 0.07±0.002 to 0.08±0.002 mm. The difference in the thickness of these formulations might be because of the different solvents used for casting of the film. When water was used as a solvent, thickness was found to be at a minimum of 0.07±0.002 mm and with increase in the amount of IPA, the thickness of film was found to increase. The low standard deviation values for the thickness of these formulations confirmed the efficiency of the method that was employed for formulation of the films.

All the films were found to be rapidly disintegrating within 60 seconds [Table 6]. The observed disintegration time was in the order F2>F3>F4>F5>F1. It was observed that the *in vitro* disintegration time was directly proportional to the thickness of the film and nature of the solvent.

From the results of mechanical properties, as given in Table 4, it was observed that formulation F1 was found to have acceptable mechanical properties as compared with formulations F2, F3, F4, and F5. This may be because of the HPMC 5 cps which got completely dissolved in the water and showed hard and tough characteristics, but in the presence of IPA, alone or in combination, it showed soft and weak characteristics. A suitable mouth-dissolving film requires moderate folding endurance, tensile strength, and percentage elongation. So the formulations F2, F3, F4, and F5 were not studied further as they failed at the first stage itself.

From the data given in Table 5, it is observed that all the formulations got separated from the surface and were found to be nontacky. From the visual appearance of the surface of the film, it was noted that formulations F1a, F1b, and F1c were found to have a smooth surface and formulation F1d had a rough surface; this might be because of the low solubility of HPMC 5 cps in water which imparted roughness to the film.

The thickness of all formulations was found to be in the range of 0.063±0.025 mm to 0.09±0.002 mm [Table 5]. The difference in the thickness of these formulations might be due to the different viscosities of the solution which were used to formulate the films. The low standard deviation values for the thickness of these formulations confirmed the efficiency of the method that was employed for formulation of the films.

In vitro disintegration test was performed for all the formulations and they were found to be disintegrated within 60 seconds. The best disintegrating time was observed for formulations F1a and F1b, whereas formulation F1d was ranked last, where disintegration time was concerned. Therefore, from the results obtained it might be concluded that formulations having a higher viscosity and thickness, that si, F1c and F1d had a comparatively high disintegration time as given in Table 5.

Films of size 3×10 mm^2 were taken for the study. From the results, it was clear that when the viscosity increased,

Table 4: Evaluation of mouth-dissolving films of *Withania somnifera* Linn to study the effect of solvent

Properties of films	F1	F2	F3	F4	F5
Film-forming capacity	Very good	Poor	Average	Average	Average
Appearance of film	Smooth, translucent	Rough	Rough	Rough	Rough
Tack test	Nontacky	Nontacky	Nontacky	Nontacky	Nontacky
Thickness (mm)	0.07±0.002	0.08±0.002	0.075±.002	0.072±0.002	0.07±0.002
Disintegration time (sec)	18±0.43	56±0.29	42±0.83	27±0.14	25±0.71
Folding endurance	20.12±0.41	2.78±0.49	7.23±0.84	10.87±0.91	15.54±0.37
Tensile strength (N/mm^2)	18.72±0.93	1.98±0.43	4.84±0.29	6.26±0.47	10.37±0.86
Percentage elongation (%)	85±0.41	12±0.75	16±0.07	37±0.20	54±0.92

the tensile strength of film also increased. Formulation F1c showed the maximum folding endurance, tensile strength, and percentage elongation. Table 5 shows the results for all the batches. Formulation F1a, with lower viscosity, was found to have folding endurance of 8±0.45 and as the viscosity of solution was increased, the folding endurance was improved to a certain extent as shown in formulations F1a, F1b, and F1c, and it again decreased in the later formulation F1d. Similar observations were noted for tensile strength; in formulations F1a, F1b, and F1c, tensile strength was found to be 8.28±0.49, 12.63±0.27, and 16.98±0.46, respectively, and for formulation F1d it was 13.09±0.46 N/mm^2. The percent elongation for all formulations was found to be in the range of 23.55±0.40% to 45.12±0.26%. The percentage elongation of the films increased linearly with increase in viscosity of the solution used for casting of the film.

As the formulation F1b had adequate physical properties, moderate folding endurance, tensile strength, and percentage elongation with minimum *in vitro* disintegration, it was selected for further studies of drying temperature.

From Table 6, it is noted that drying temperature was directly proportional to drying time.

Determination of film-forming capacity, visual appearance, and tackiness for all the formulations are shown in Table 6. It was observed that all the formulations were found to be nontacky to each other, except formulation F1bi. This might be because of the presence of moisture in it which may not completely evaporate when film-dried at 60–65°C.

The thickness of the formulation was 0.07±0.002 mm. The low values for standard deviation indicate physical uniformity of the membranes.

All the films were found to be rapidly disintegrating within a span of 18 to 20 seconds [Table 6]. The observed *in vitro* disintegration time was in the order of F1bii >F1biii = F1biv>F1bi. It was observed that the drying temperature did not have much influence on *in vitro* disintegration time of the film.

From the results of folding method, tensile strength, and percentage elongation given in Table 6, it was found that increase in temperature was inversely proportional to folding endurance, tensile strength, and percentage elongation. Therefore, the film dried at 60–65°C had excellent mechanical properties with folding endurance (56±0.68), tensile strength (20.21±0.37 N/mm^2), percentage elongation (83.08±0.28%), and *in vitro* disintegration (18±0.35 sec) as compared with all other formulations. But the time required to dry the film was more, that is, 60 minutes and the film was found to be slightly tacky when stacked upon each other. Therefore, the formulation F1bii was found to be the most acceptable having comparatively less drying time (40 min), with desired physical properties having folding endurance (49±0.25), tensile strength (18.74±0.48 N/mm^2), percentage elongation (72.08±0.29%), and *in vitro* disintegration time (20±0.84 sec).

CONCLUSION

The main objective of this research work was to study the effect of the nature of the solvent used for casting of the film, effect of drying temperature, and viscosity of the solution on mouth-dissolving film of *W. somnifera* Linn. From the

Table 5: Evaluation of mouth-dissolving films of *Withania somnifera* Linn at different viscosities

Formulation code	F1a	F1b	F1c	F1d
Film-forming capacity	Very good	Very good	Very good	Very good
Appearance of film	Smooth	Smooth	Smooth	Rough
Tack test	Nontacky	Nontacky	Nontacky	Nontacky
Thickness (mm)	0.063±0.025	0.07±0.0002	0.082±0.0002	0.09±0.002
Disintegration time (sec)	18±0.3	18±0.28	24±0.37	30±0.48
Folding endurance	8±0.45	15±0.36	24±0.54	19±0.43
Tensile strength (N/mm^2)	8.28±0.49	12.63±0.27	16.98±0.98	13.09±0.46
Percentage elongation (%)	23.55±0.40	30.87±0.81	37.87±0.29	45.12±0.26

Table 6: Evaluation of mouth-dissolving films of *Withania somnifera* Linn when dried at different temperatures

Formulation code	F1bi	F1bii	F1biii	F1biv
Drying time (min)	60	40	30	15
Separation from the surface	Good	Very good	Very good	Very good
Appearance of film	Smooth film	Smooth film	Smooth film	Smooth film
Tack test	Tacky	Nontacky	Nontacky	Nontacky
Thickness (mm)	0.07±0.002	0.07±0.002	0.07±0.002	0.07±0.002
Disintegration time (sec)	18±0.35	20±0.84	19±0.38	19±0.15
Folding endurance	56±0.68	49±0.25	27±0.89	20±0.24
Tensile strength (N/mm^2)	20.21±0.37	18.74±0.48	10.00±0.23	5.84±0.28
Percentage elongation (%)	83.08±0.28	72.08±0.29	59.78±0.12	42.76±0.49

physicomechanical and *in vitro* dissolution data obtained, it was confirmed that selected process variables have a potential influence on these properties. When HPMC 5 cps was used as a film former, water was found to be an excellent solvent for casting of the solution. From the present study, it was also observed that 8,500–9,000 cps of viscosity was required to formulate the best-quality film with minimum variations in thickness. When mouth-dissolving film of *W. somnifera* Linn was dried at 80–85°C, it showed the most favorable physicomechanical proprties.

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