

Original Article

APPLICATION OF *IPOM OEA BATATA* STARCH MUCILAGE AS SUSPENDING AGENT IN
OSELTAMIVIR SUSPENSION

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ABSTRACT

Objective: The objective of the study was to search for a cheap and effective natural raw material that can serve as an alternative suspending agent in the formulation of oseltamivir suspension. The phytochemical and the physicochemical properties of the mucilage of *Ipomoea batata* starch were studied.

Methods: The suspending properties of mucilage extract of *I. batata* starch was evaluated comparatively with that of acacia, xanthum gum and sodium alginate using model formulations at concentrations of 0.75, 1.5 and 3.5% w/v. The Prepared suspensions were evaluated by studying different parameters like pH, sedimentation volume, redispersibility, Flow rate (F), viscosity, degree of flocculation, effect, effect of temperature and stability studies.

Results: The results showed the presence of flavonoids, saponin, protein, carbohydrate and reducing sugars. The rheological properties of suspension showed that As the concentration of suspending agent increased viscosity also get increased which reduces the sedimentation and contributes to the stability of suspension. Increase in viscosity avoids the particle aggregation so particles remain in a flocculated state. While an increase in temperature did not significantly increased the viscosity of suspension. The order of stability of suspension in terms of sedimentation profile ranked thus: OF3 (3%w/v IBSM)>OF12 (3%w/v SA)>OF6 (3%w/v AG)>OF9 (3%w/v XG)>B (5%w/v potato starch).

Conclusion: These results indicate that mucilage from *I. batata* starch in oseltamivir suspension has low sedimentation rate, medium viscosity and easily dispersible and can therefore serve as suspending agent in formulations of suspensions of sparingly soluble drugs.

Keywords: Oseltamivir, Suspension, Sedimentation volume, redispersibility, flocculation.

INTRODUCTION

In recent era, oral drug delivery is most prominent route amongst all other routes of drug administration [1]. Since long years, an oral pharmaceutical suspension has been one of the most preferable dosage forms for pediatric patients or patients incapable to tolerate solid dosage forms [2, 3]. A Pharmaceutical suspension is a coarse dispersion in which an internal phase is dispersed uniformly throughout the external phase [4]. Suspension is thermodynamically unstable, so it is necessary to add suspending agent which reduces the rate of settling and permits easy redispersion of any settled particulate matter both by protective colloidal action and by increasing the consistency of the suspending medium [5, 6].

Suspending agents are grouped into three classes: synthetic, semi synthetic and the natural polysaccharides, in which class acacia, tragacanth and starch belong to the latter class (Mbang *et al.*, 2004; Mahmud *et al.*, 2010). Natural suspending agents are mainly used as they are biodegradable and biocompatible [7]. Use of natural suspending agents likes okra gums [8], *Abelmoschus Esculentus* Mucilage [9], *Cassia tora* Mucilage and *Trigonella foenum graecum* Mucilage [10] to formulate suspension of Active pharmaceutical agents, has been previously reported. *Ipomoea batata* is a creeping plant with gnarled stems and adventitious roots. The stem is green or purple, pubescent, some of their roots are tubers rich in starch and sugars, which are used in food, belong to the family Convolvulaceae, commonly called as sweet potato or chilagada dumpa.

Oseltamivir [(3R-(3 α ,4 β , 5 α)]-ethyl4-(acetylamino)-5-amino-3-(1ethylpropoxy)1cyclohexene-1-carboxylate phosphate) is a Neuraminidase Inhibitor. It is a white crystalline solid substance and its chemical structure is as in fig. [11]. It is used for the symptomatic treatment of uncomplicated acute illness caused by susceptible influenza A or B virus in adults, adolescents, and children 1 y of age or older who have been symptomatic for no longer than 2 d.

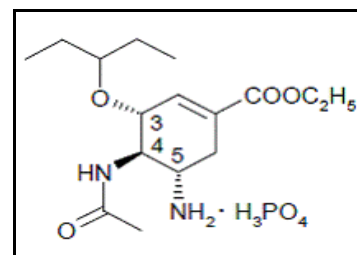


Fig. 1: Structure of oseltamivir phosphate

MATERIALS AND METHODS

Materials

Oseltamivir was obtained as a gift sample. *Ipomoea batata* tubers and Tutti-Frutti flavor were purchased from local market. All other solvents used were of analytical grade.

Methods

Extraction of starch from *Ipomoea batata* (Tubers)

The fresh tubers are subjected to thorough washings and peel off their skins. The resultant tubers were chopped and crushed in a blender to a pasty mass using sufficient amount of water. The pasty mass was diluted in water, filtered using the muslin cloth to remove pulpy mass. The filtrate is collected and kept a side for 1h. The supernatant liquid is decanted to give crude starch. The crude starch was washed with water 2 times until free from fibers. The purity of starch is confirmed by homogeneity test with iodine. The resultant starch is dried in an oven, at 50 °C for 24 h [11].

Preparation of suspending agent from *Ipomoea batata* Starch

16.2 gm of starch was taken in a beaker and 24 ml of hot water, was added and stirred well to make suspension and heated in a boiling

water bath with continuous stirring until a translucent paste is formed. It has been observed that during paste formation, not all of the starch is hydrolyzed [12, 13].

Evaluation of mucilage

Determination of swelling index

500 mg of isolated mucilage was taken in a Petri dish and then 10 ml of distilled water was added and the mixture was shaken and allowed to stand for 1 hour. After 1 hour the remaining water in Petri dish was discarded and the weight increase of the isolated mucilage was determined [14, 15].

$$\frac{W2-W1}{W1}$$

$$\text{Swelling Index \% (SI)} = \frac{W2-W1}{W1} \times 100 \dots\dots (1)$$

W1= Weight of compact at time '0'

W2=Weight of compact at time 't'.

Phytochemical screening of mucilage

Preliminary tests were performed to confirm the nature of mucilage obtained. The chemical tests that were conducted are: Molisch's test, Ninhydrin test, Wagner's test, Ruthenium red test, Iodine test, Shinoda test, Keller-Killaini test and Ferric chloride test [16, 17].

Table 1: Composition of oseltamivir suspension

Ingredients	Batch code											
	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9	OF10	OF11	OF12
Oseltamivir(mg)	6	6	6	6	6	6	6	6	6	6	6	6
I BSM(mg)	0.75	1.5	3	-	-	-	-	-	-	-	-	-
Acacia Gum(mg)	-	-	-	0.75	1.5	3	-	-	-	-	-	-
Xanthum Gum(mg)	-	-	-	-	-	-	0.75	1.5	3	-	-	-
Sodium Alginate(mg)	-	-	-	-	-	-	-	-	-	0.75	1.5	3
Sorbitol(mg)	174.5	173	171.5	174	173	171.5	174.5	173	171.5	174.5	173	171.5
Monosodium citrate(mg)	11	11	11	11	11	11	11	11	11	11	11	11
Sodium saccharin(mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol(ml)	2	2	2	2	2	2	2	2	2	2	2	2
Tuiti-fruity flavor(mg)	2	2	2	2	2	2	2	2	2	2	2	2
Titanium dioxide(mg)	4	4	4	4	4	4	4	4	4	4	4	4
Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200	200

Micromeritic properties of mucilage

Bulk density and tap density

Accurately weighed mucilage was poured in 100 ml graduated cylinder. The volume occupied by mucilage, before (Vb) and after tapping (Vt) was determined in triplicate using bulk density apparatus (Lab Hosp, Mumbai, Maharashtra, India). The bulk density and tap density was calculated using the formulas [18, 19]

$$\text{(Bulk Density)BD} = \frac{M}{Vb} \dots\dots (2)$$

$$\text{(Tapped Density)TD} = \frac{M}{Vt} \dots\dots (3)$$

Angle of repose, carr's compressibility index (CCI) and Hausner's Ratio (HR)

Angle of Repose, (CCI) and (HR) were determined using following equations [20, 21]

$$\theta = \tan^{-1} H/R \dots\dots\dots (4)$$

Where, 'θ' is angle of repose; 'H' is height between lower tip of the funnel and the base of heap of powder; and 'R' is radius of the base of heap formed

$$CCI = \frac{BD - TD}{TD} \times 100 \dots\dots\dots (5)$$

$$HR = \frac{TD}{BD} \dots\dots\dots (6)$$

Where, TD and BD are tapped density and bulk density respectively.

Formulation of oseltamivir suspension

Oseltamivir suspensions containing 6% w/v of Oseltamivir were prepared using *Ipomoea batata* starch mucilage, acacia gum, xanthum gum and sodium alginate starch (0.75, 1.5 and 3%) as the suspending agents as shown in table 1. Mucilages of the suspending agent were prepared by hydration using part of the vehicle. The solid components of the formulation were finely triturated with the aid of mortar and pestle. The suspending agent was added to the

powdered drug and triturated until homogeneous slurry was obtained. Mono sodium citrate (11%) was used as the preservative and saccharine (0.5%) was used as the sweetener. This was transferred into a 100 ml beaker and the remaining vehicle was used to rinse the mortar to make up the required volume [27, 28].

Evaluation of suspension

pH determination

The pH of all developed formulations was measured using digital pH meter.

Sedimentation volume

Sedimentation volume is determined by following equation [22].

$$F = \frac{Hu}{Ho} \dots\dots\dots (7)$$

Where, Hu is ultimate or final height of sediment as suspension settles, Ho is original height of suspension.

Redispersibility

Fixed volume of each suspension (50 ml) was kept in calibrated tubes which were stored at room temperature for various time intervals (1, 5, 10, 15, 20, 30, 45 d). At regular interval one tube was removed and shaken vigorously to redistribute the sediment and the presence of deposit if any was recorded [23].

Flow rate (F)

The time taken for 10 ml sample of suspension to flow through a 10 ml pipette was determined and the flow rate calculated using the following equation:

$$F = \text{Volume of pipette (ml)} / \text{Flow time (sec)} \dots\dots\dots (8)$$

Determination of viscosity

The viscosity of suspension samples was determined using the Brookfield viscometer at 100 rpm. All determinations were carried out in at least triplicates and results obtained were expressed as the mean values [24].

Degree of flocculation

Degree of flocculation (β) was determined using following equation.

$$\beta = \frac{(Vu)_{floc}}{(Vu)_{defloc}} \dots \dots \dots (9)$$

Where, $(Vu)_{floc}$ is ultimate sedimentation volume in flocculated suspension and $(Vu)_{defloc}$ is ultimate sedimentation volume in deflocculated suspension.

Effect of temperature

Further, the effect of the temperature (30° to 60°) was investigated on the viscosity of the suspension of all formulations.

Drug content

10 ml of suspension (20 mg/ml) was accurately measured and transferred into 100 ml volumetric flasks. And volume made up with 0.1 N HCl. Further from above suspension 1 ml was withdrawn and added to 10 ml flasks, volume made with 0.1 N HCl. Absorbance was measured using UV-Visible double beam spectrophotometer (shimadzu) at λ_{max} 620 nm. Drug content was calculated by comparing the absorbance with standard curve [25]

Particle size measurement

Particle size determination is carried out by optical microscopy method using motic microscope. Suspension was spread on slide and observed under the microscope. Diameters of 20 particles were measured.

In vitro dissolution studies

Dissolution study of formulated suspensions (n=3) was carried out in USP type II dissolution test apparatus (TDT 08 L, Electrolab, Mumbai, India) in 500 ml of water for 30 min (37±0.5 °C and 25rpm). USP type II dissolution test apparatus although mainly

designed for tablets and capsules, this apparatus has also been used by several investigators to study the dissolution behavior of suspensions. 10 ml suspension was introduced carefully into the bottom of the apparatus. 5 ml aliquots were withdrawn at the interval of 5 min for analysis and replenished by equivalent amount of blank. The aliquots were filtered through Whatman filter paper and further analyzed at the respective wavelength by double beam UV visible spectrophotometer (shimadzu). The data obtained were put in PCP Disso V 3.0 (Pune, India) software to type the drug release kinetics [26].

RESULTS AND DISCUSSION

Evaluation of mucilage

Determination of swelling index

Swelling index of *Ipomoea batata* was found to be 38% at end of 1 hr. Result shows that the swelling index was found to be increased with time. Swelling index was increased, because weight gain by mucilage was proportional to the rate of hydration. The direct relationship was observed between swelling index and mucilage concentration, as mucilage concentration increase swelling index increased.

Phytochemical screening of starch mucilage

Phytochemical tests carried out on *Ipomoea batata* starch mucilage confirmed the absence of alkaloids, glycosides starch and tannins. Treatment of mucilage with ruthenium red showed red coloration confirms the obtained product as mucilage. A violet ring was formed at the junction of two liquids on reaction with Molisch's reagent indicating the presence of carbohydrates. The results of phytochemical screening of mucilage are summarized in table 2.

Table 2: Phytochemical screening of *Ipomoea batata* starch mucilage

S. No.	Identification test	Name of test	Observation
1	Test for Carbohydrates	Molisch's test	Positive
2	Test for proteins	Ninhydrin test	Negative
3	Test for alkaloids	Wagner's test	Negative
4	Test for mucilage	Ruthenium red test	Positive
5	Test for starch	Iodine test	Positive
6	Test for flavonoids	Shinoda test	Negative
7	Test for glycosides	Keller-Killaini test	Negative
8	Test for tannins	Ferric chloride test	Negative

Table 3: Micromeritic properties of *Ipomoea batata* starch mucilage

Parameter	Value
Bulk density	0.7g/ml
Tap density	0.89 g/ml
Hausner's ratio	1.32
Carr's Compressibility Index(CCI)	24.7
Angle of Repose	25.69 °

Micromeritic properties of starch mucilage

Values of Hausner's ratio, CCI Angle of Repose showed that mucilage powder has excellent flow properties. Micromeritic properties of mucilage have been summarized in table 3.

Evaluation of suspension

Batch C1 and C2 was found to be disturbed at an initial phase so not consider for further evaluation. This could attribute to the low viscosity of the suspension.

pH determination

pH of all formulation was found to be in the range of 7.01–7.31. Comparative profile of pH all batches is given table 2.

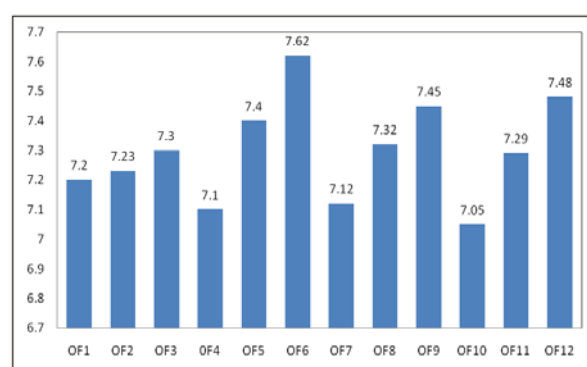


Fig. 2: Comparative pH profile for all batches of suspensions

Sedimentation volume

Sedimentation volume was found to be decreased at the end of 7 d. Result of values of Sedimentation Volume is reported in graph 1. Batch C6, C7 and C8 were found to be stable and dispersed at the end of 45 d. The dispersed particle was sediment at the faster rate in suspension containing the lower concentration of suspending agent compared to containing higher amount (fig. 3).

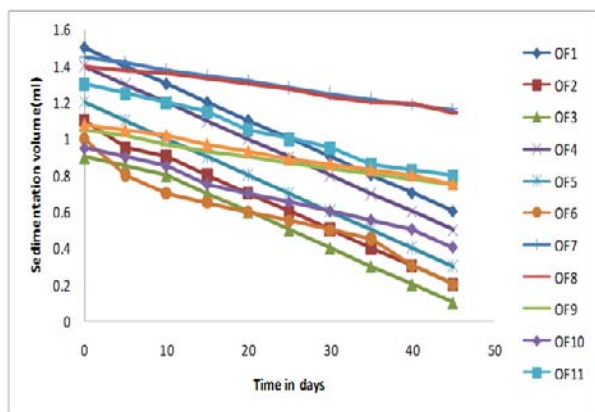


Fig. 3: Comparative sedimentation volume profile of suspensions

Redispersibility

Since the suspension sediment on storage, it must be radially dispersible so as to ensure a more uniform dosage administration of medicament after shaking. Suspension is called as caked if sediment

remains after vigorous shaking. All the suspension was found to be easily redispersible after maximum 13 shaking after 45 d (table 4). Redispersibility was found to be faster for suspension with lower amount of suspending agent comparing to higher concentration. This may attribute to the higher viscosity of these suspensions with higher concentration.

Flow rate (F)

Flow rate was found to be decreased as concentration of suspending agent and viscosity of suspension increased. It is found in the range of 0.1-0.05 (table 4).

Determination of viscosity

Viscosity of all formulation was found to be decreased with increasing rpm indicated shear thinning nature of suspension. Values of viscosity for all batches have been reported in table-4.

Degree of flocculation

Degree of flocculation was determined for all formulated suspension using different concentration of *Ipomoea batata* starch mucilage. The values of the degree of flocculation for all formulated suspension have been mentioned in table 4 and it found to be increased at the higher concentration of suspending agent. This is due to the higher viscosity of suspension at higher concentration, which ultimately reduces the sedimentation of suspension.

Table 4: Evaluation of suspension

Ingredients	Batch code											
	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9	OF10	OF11	
Particle size(um)	26.3	24.3	21.5	26.3	24.3	21.5	26.3	24.3	21.5	26.3	24.3	21.5
Degree of flocculation	2.5±0.12	3.6±0.2	4.3±0.1	2.1±0.2	3.1±0.12	4.02±0.08	0.2±0.2	3.3±0.2	4.2±0.06	2.3±0.4	3.4±0.16	4.1±0.21
Flow rate	0.32	0.24	0.18	0.28	0.22	0.1	0.25	0.18	0.9	0.3	0.23	0.14
No. of shaking for complete dispersion	06	08	11	07	09	13	06	09	12	07	09	12
Drug content	96.4±0.08	97.2±0.18	99.8±0.15	96.8±0.19	97.4±0.12	99.16±0.11	96.2±0.14	96.8±0.25	98.9±0.18	95.8±0.18	97.4±0.2	98.1±0.14
Viscosity (poise)	1245	1262	1269	1254	1269	1273	1252	1267	1271	1248	1265	1269

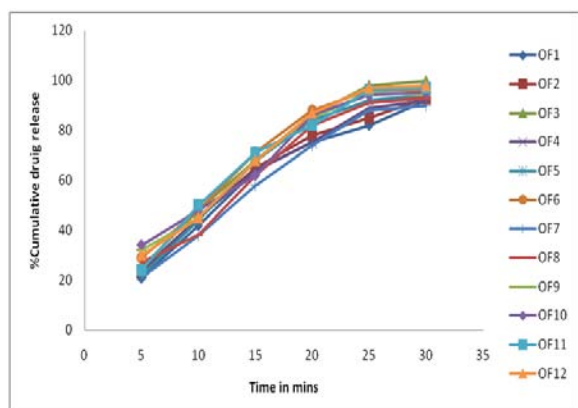


Fig. 4: Plot of % cumulative drug release Vs time (min) of different batches of suspensions

Effect of temperature suspension

Increase in temperature reduces the viscosity for all formulation.

Drug content

Drug content for all batches was found to be in the range of 95-99%.

Particle size measurement

Particle sizes of 20 particles of all formulated suspensions were determined and values are reported in table 4.

In vitro dissolution studies

Result showed that all formulation releases almost 95% drug at the end of 30 min. For most of the batches, the release kinetics of ciprofloxacin from the suspensions appeared to follow first order release kinetics. Some batches also follow Korsmeyer peppas kinetic model (n= 0.47) (fig. 4).

CONCLUSION

Formulated oseltamivir suspension with natural suspending agent i.e. *Ipomoea batata* starch showed superior stability over the period of time. Increase in concentration of suspending agent increases the viscosity of suspension which ultimately reduces sedimentation and contributes to the stability of suspension.

CONFLICT OF INTERESTS

Declared None

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