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Influence of Organic pH Modifiers on Molecular Interactions and Sustained Release of Methyl Eugenol in Angstrom Void Polymer (AVP) Gel Matrix Formulation

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ABSTRACT: Methyl eugenol (ME) is widely used as fruit fly attractant in infested agricultural fields. But the biggest challenge is to develop sustained release formulation for slow and sustained release of ME, which can be effectively used for prolonged period when deployed in open fields. In the present study evaluating sustained release activity of ME using Angstrom Void Polymer (AVP) gel matrix formulation, the experimental results depicted that the pH of AVP gel matrix influences ME molecules to exhibit variable weak ionic attraction forces with acrylic acid units of the polymer gel as well as the surface adsorption, influx, and efflux movement of ME from the 3D molecular sieves of zeolites 4A. This behaviour of ME significantly influences the sustained release property of ME loaded AVP gel matrix. In the present study, ME charged Carbopol 940 gel formulation when coupled with ME charged Zeolites 4A, and the resultant matrix modulated with organic pH modifiers, the experimental results showed a significant increase in sustained release activity of the matrix. The experimental results exhibited that ME release rate was influenced by changes in pH of the matrix, which alters the amphoteric nature of the Zeolites 4A and influences the changes in attractive forces between ME and Zeolites 4A also ME interaction with Carbopol 940 gel in the matrix. The present experimental results clearly demonstrate the relationship between pH and sustained release property of the AVP gel matrix for ME. The results clearly demonstrated, when pH changes from more acidic to less acidic it improves the sustained release property of the matrix and at less acidic 6.5 pH sustained release effect of ME was optimal and exhibited a sustained release of ME with an average release of 33.33±0.06mgs per day effectively for 56 days, with a loading dose 2gms of ME into the zeolite 4A dispersed Carbopol 940 gel; AVP gel matrix formulation (Indian patent applied; Patent Application Number: 201741016813).

Keywords: Methyl Eugenol (ME), Carbopol 940 gel, Zeolites, AVP gel matrix.

INTRODUCTION

Newer sustained release formulations for the pheromone-based pest control are gaining importance in recent days. Scientific community facing challenges while developing the newer formulations, as these formulations were deployed in the harsh environmental conditions of the open-air agricultural fields. It is very essential to adapt chemically mediated sustained release effect, so that the release rates could be controlled and altered to meet the required objective of sustained release effect.

Number of sustained release formulations using organic matrix were developed earlier adopting moisture influenced surface degradation, slow diffusion of the pheromones from gels or solids, film coating, and other techniques to promote sustained release effect and to control the release rates. As these pheromone-based formulations were deployed in the open agricultural fields, the harsh environmental conditions limit its application, and the desired sustained release activity was rarely achieved. Carbopol polymers are with variable molecular weight, highly cross linked, acrylic acid polymers. The high molecular weight, degree of cross linking and its good water retention properties makes them a suitable matrix for gel formulations. This functionally diverse performance of Carbopol gel matrix can provide a sustained release activity for the incipient (CBC Co., Ltd., 1999; Taylor and Bagley 1977; Taylor and Bagley 1977a).

The unique property of Carbopol polymers to readily absorb water influenced by the pH of the medium, gets quickly hydrated, swells, and forms gels with variable rheology. Carbopol polymers are hydrophilic in nature and being a water insoluble polymer due to its high cross-linking nature, they form a good matrix for the sustained release drug delivery system. Carbopol gels are extensively used as medium for the sustained release formulations in drugs and cosmetic industries

(Taylor and Bagley 1975, Taylor and Bagley 1977; Taylor and Bagley 1977a; Nae and Reichert 1992). The unique property of both natural zeolites and chemically modified zeolites with tailor made properties makes them suitable candidature for various industrial applications. These tailor-made properties of the zeolites with its unique 3D porous framework with variable Si/Al ratio, amphoteric nature of Alumina and silica explored to control the sorption of organic molecules in their cages (Balkus and Gabrielov 1995; Corma 1992; Zou *et al.,* 2005, Conradsson *et al.,* 2000) . The unique properties of zeolites enable the inward and outward movement of molecules through 3D framework of molecular sieves under the influence of moisture, pH, and temperature of the surrounding system (Libau, 1985; Baerlocher *et al.,* 2007; Stuckenschneider and Schembecker 2014).

In the present experiment, a distinctive approach was adopted in combining the ME impregnated Carbopol 940 gel and ME sorbed Zeolites 4A, the combined matrix was evaluated for the synergistic sustained release of ME under the influence of pH of the medium to deploy the resultant formulation in the fruit fly infested agricultural fields.

MATERIALS AND METHOD

Active pheromone ingredient (API), ME of 95% purity, was procured from in-house Advanced Pheromone development (APD) department, Barrix Agro Sciences, Molsieve-13X, Molecular Sieve Zeolites of 2-4mm (Zeolites 4A), the specific variant was obtained from Gujarat Multi Gas Base Chemicals Pvt. Ltd., Carbopol-940 was purchased from s d fine-chem limited. All the other chemicals and reagents used in the experimental work were of analytical grade.

A. Experimental

Zeolites 4A pellets were selected and procured after judging the pellets size, Al/Si ratio, pore size and the nature of 3D framework of molecular sieves. The selected Zeolites 4A were activated by dry heating the zeolites in a tray at 150°C for half hour in hot air oven.

B. Preparation of ME loaded Angstrom Void Polymer gel matrix formulation.

Calculated quantity of ME dissolved in organic solvent, stabilised by the addition of antioxidant and UV stabilizer, was added to the container containing specific quantity of activated Zeolites 4A and allowed to stand for 1hr. for complete absorption. The contents of the container were blended thoroughly, confirming the complete sorption of ME into the molecular sieves of the Zeolite 4A.

ME charged Carbopol 940 aqueous gel was prepared separately by slowly adding alkalised purified water to the polyacrylate 940 (Carbopol 940). The mixture was continuously stirred and allowed to swell, after gelation the gel was stabilized by the addition of antioxidant and photo stabilizer. To the resulting gel moisture retaining agent was added with continuous stirring to ensure uniform mixing. Finally, calculated quantity of ME was slowly added into the Carbopol 940 aqueous gel with continuous stirring. The gel was stirred for 30min to ensure the uniform dispersion of ME.

The prepared Pheromone charged Zeolites 4A was slowly incorporated into the aqueous Carbopol 940 gel. After thorough blending, desired pH of the matrix was adjusted using either an organic acid and or organic base. The AVP gel matrix so prepared was stirred for 30min to ensure the uniform spreading of Zeolites 4A in the gel, forming ME charged Angstrom void polymer (AVP) gel matrix formulation.

The formulations were deployed in the open field area and the ME release rates were experimentally determined using Agilent Gas Chromatography (GC) 7890 B series with Flame Ionization Detector (FID) under the following chromatographic conditions using methanol (GC grade) as blank (Table 1).

The residual quantity of the ME in the AVP gel matrix formulation was estimated at regular intervals and the results were recorded to assess the impact of pH on molecular interactions of ME with organic Carbopol 940 aqueous gel and with inorganic Zeolites 4A. The results clearly established pH influenced sustained release of ME from AVP Gel matrix.

Table 1. Chromatographic conditions.

GC Column	HP5, 30m × 0.32mm; 0.25µm film thickness
Injection temperature	225°C
Detector temperature	275°C
Oven temperature	110°C Hold for 1 minute
Ramp temperature 1	With 5°C/minute to 120°C & hold for 1minute
Ramp temperature 2	With 30°C/minute to 220°C & hold for 0.6667 minute
Total Run time	8 minutes
Constant flow	3ml/min
Split ratio	1:20
Injection Volume	1µl

RESULTS AND DISCUSSION

Numerous Carbopol gels, either using Carbopol alone or in combination with other gelling agents were earlier prepared and reported for the sustained release of drugs and pharmaceuticals, none reported the formulations developed for the sustained release of pheromones, prepared using Carbopol polymer. In the present study, efforts were made to develop a sustained release ME formulation, using a combination of ME loaded Carbopol 940 gel and Zeolites 4A. The resultant ME loaded AVP gel matrix formulation to be deployed in open agricultural fields for effectively attracting the fruit flies for 56 days. Weak ionic interactions and weak

attraction forces between organic molecules (ME) with the matrix of organic polymeric gel containing Zeolites 4A was influenced by the presence of ionisable hydrogen ions, changes induced in dipole interactions, weak hydrogen bonding and Lewis acidic properties of the matrix. These molecular interactions of ME were influenced by the pH of the surrounding medium.

Thus, pH influences and induces the changes in the dipole interactions for the free acid terminals of the polymerised acrylic acid units in the Carbopol gel and in turn influences how strongly the ME molecules are bound to the gel. The similar behaviour of ME was observed in the inorganic Zeolites 4A matrix, where the amphoteric nature and Lewis's acid-base behaviour of both alumina (Al_2O_3) and poly silicon dioxide (SiO_2) influences both surface adsorption and the intrusion of the ME molecules into the 3D network of molecular sieves present in the Zeolites 4A. The amphoteric behaviour of zeolites, adsorption, and intrusion of ME into the 3D molecular sieves was influenced by the pH of the surrounding medium. The Al/Si ratio coupled with Lewis's acid-base behaviour of the Zeolites 4A and with weak hydrogen bonding and attraction forces of Carbopol 940 gel synergistically influences and significantly contributes to the slow, sustained and control release of ME into the surrounding environment (Fig. 1).

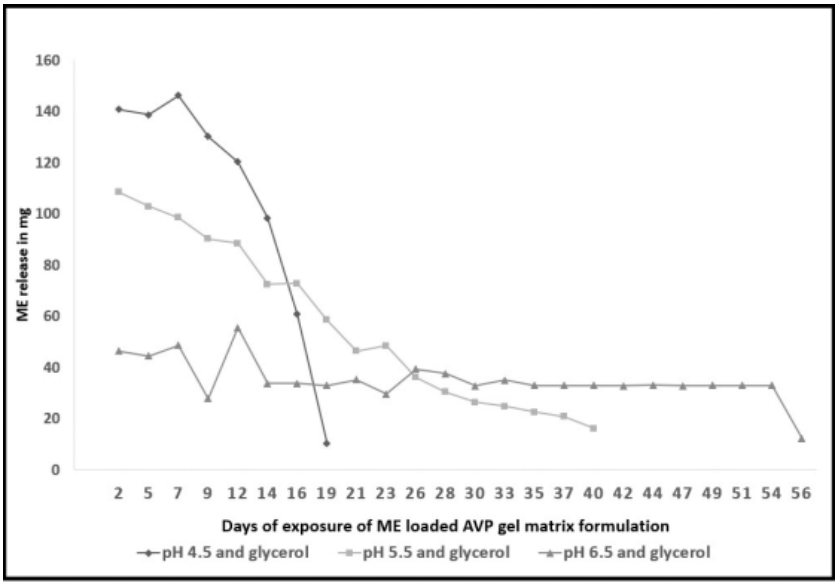

Fig. 1. Influence of pH on ME release rate in AVP gel matrix.

In the present experiment Angstrom void polymer (AVP) gel matrix formulation showed an erratic release of ME for a period of 19 days at pH 4.5 with high daily release potential of 140mgs initially and later dropped to 80mgs (Fig. 1). Whereas the release rate was slow and sustained but not constant release at pH 5.5 also with high daily release potential of 110mgs initially and later dropped to 45mgs on 26th day but extended for a period of 40days. The results were surprised at pH 6.5, where the AVP gel matrix showed a slow, sustained, extended and almost constant release rates for the ME. The AVP gel matrix showed a slow, sustained, constant and extended release of ME with an average release of 33.33±0.06 mgs per day effectively for 56 days, with a loading dose 2gms of ME into the zeolite dispersed Carbopol gel, angstrom void polymer (AVP) gel matrix formulation making it a novel gel formulation.

Carbopol 940 was used in the preparation of controlled-release drug formulations (AHMS 2020). Behaviour of Carbopol solutions with changes in pH during gel formulation stage, affecting its rheology in which NaOH was added as a stabilizer was reported (Fernando *et. al.,* Conference: 26th ABCM ICME 2021). pH influenced gels containing sulfacetamide sodium for improved pharmacological effect was reported by Sheshala *et al.* (2019). Kaur *et al.* (2014) reported that release of Glibenclamide by transdermal gels can be prepared using a combination of Carbopol and β-cyclodextrin.

CONCLUSIONS

Present experimental results clearly demonstrate the direct relationship between pH of the Carbopol 940 aqueous gel and its impact on Zeolites 4A for the molecular intrusion, influx, and efflux of ME molecules from the 3D molecular sieves as well as surface adsorption property for ME. Thus, by modulating the pH of the AVP gel matrix system, in and out movement of ME from the molecular sieves of Zeolites 4A, ionic interaction, and surface adsorption of ME with AVP gel matrix can be modulated. These interactive properties of the ME depend on the chemical nature of active ingredient and pH of the matrix. In the present experimental study, sustained release activity of the AVP gel matrix was achieved for 56 days at pH 6.5 for the pheromone ME. Thus, the developed AVP gel matrix formulation can be deployed in open agricultural fields for effectively attracting fruit flies.

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Conflict of Interest. None.

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