

USE OF HONEY AS A VISCOSITY MODIFIER IN THE FORMULATION OF COTRIMOXAZOLE SUSPENSION

* AREMU, O. I., MAKANJUOLA, V. M. AND ADEDOKUN, M. O.

DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL
TECHNOLOGY, FACULTY OF PHARMACY, OLABISI ONABANJO
UNIVERSITY, SAGAMU.

ABSTRACT

A study has been carried out on honey from comb of bee, *Apis mellifera*, L. (Family, Apidae) as a viscosity modifier in conjunction with certain suspending agents, in the formulation of cotrimoxazole suspension, to solve the problem of caking associated with most brands in the market. Six formulations including control, with or without suspending agents were compared to commercial brands by determining sedimentation volume, flow rate and rheological properties of all the preparations. The results show that two out of five commercial brands had satisfactory suspendability characteristics ($p < 0.05$). The preparations with compound tragacanth and corn starch as suspending agents in conjunction with honey had a better stability profile than the others. While in case of polyvinylpyrrolidone in addition to aforementioned suspending agents in sorbitol gave a reliable suspension than the rest in this category. Generally it appears that formulations with sorbitol tend to have better suspendability indices than that of honey. There is a strong statistical significance of the effect of dispersing medium and type of suspending agent on the stability of suspensions $p < 0.05$. In addition, some of the test formulations compared favorably with commercial brands.

Keywords: honey, suspending agent, viscosity modifier, suspension, cotrimoxazole.

INTRODUCTION.

A pharmaceutical suspension is a type of disperse system, in which one substance (the dispersed phase) is distributed in particulate form throughout another (the continuous phase) (1). It is a coarse dispersion containing finely divided insoluble materials of solid particles greater than $0.1\mu\text{m}$ in diameter, suspended in a liquid medium (2). It can also be defined as preparations containing finely divided drug particles (referred to as the supenoid) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility (3).

Drugs are usually presented to patients in different forms and these are known as pharmaceutical dosage forms. There are different kinds of

pharmaceutical dosage forms, classified as solid, semi-solid or liquid. In most instances, pharmaceutical preparations are formulated so that an amount of the drug substance corresponding to the usual dose is contained in a single dose. Commercially, most drug substances are made available in more than one dosage form and several concentrations or strengths (3). Most suspensions are prepared and stored in their final containers until required for use. In other cases, where undiluted effects may be caused by prolonged contact between the solid particles and the liquid dispersion

Journal of Pharmaceutical and Allied Sciences
Vol. 7 No. 1 (2010)
ISSN: 1596-8499

Website: www.ajol.info/journals/jophas

medium, the suspension is prepared immediately before use and is accepted for only a limited period thereafter (4).

Drugs that have a very low solubility in pharmaceutically acceptable liquids are conveniently formulated as suspensions. A suspension in a suitable non-aqueous vehicle may be a useful form of administration for drugs that degrade rapidly in aqueous solution. Palatable mixtures can sometimes be made with an insoluble derivative of a drug that in its soluble form, has a highly unpleasant taste, for example, chloramphenicol can be administered to children as suspensions of chloramphenicol palmitate. (5). Suspensions therefore contribute to pharmacy and medicine by supplying insoluble and often distasteful substances in a form that is pleasant to the taste, by providing a suitable form for the application of dermatologic materials to the skin and sometimes to the mucous membrane and for parenteral administration of insoluble drugs (6). Thus, suspensions will usually provide more rapid dispersion and dissolution of the drug than either tablets or capsules, provided that the drug is in appropriate particle size, can be redispersed easily and does not settle excessively or 'cake' on storage. This could be achieved by the aid of a good thickening or suspending agent (7).

The rate at which particles in a suspension sediment is related to their size, density and viscosity of the dispersion medium. The various factors involved in the rate of velocity of settling of the particles in a suspension are embodied in Stoke's law equation (2) (Eqn 1).

$$V = \frac{2r^2(d_1 - d_2)g}{9\eta}$$

where V = The velocity of the fall of a spherical particle

g = Gravitational constant

d_1 and d_2 = density of the particle and the liquid respectively in g/ml:

r = particle radius

η = the viscosity of the medium in poises.

The manipulations of any parameters above can aid the stability of suspensions or otherwise.

Most brands of co-trimoxazole suspension have problems of rapid settling of suspended particles with a resultant problematic 'caking'. Honey is a thick, syrupy, translucent, pale yellow or yellowish-brown liquid, obtained from bee, *Apis mellifera*. L. (Family Apidae). It has a pleasant characteristic odour. When heated on a water-bath, the odour becomes pronounced but is otherwise unchanged. The taste is sweet and characteristic, varying according to the origin. Purified honey contains 70 to 80% of glucose and fructose, the ratio of fructose to glucose usually being slightly greater than 1 to 1, together with water, sucrose, dextrin, wax, proteins, volatile oil, and formic acid (7).

In the present work, honey obtained from the comb of the hive bee, was used as a viscosity modifier in co-trimoxazole suspension.

MATERIALS AND METHODS

Materials used were sulphamethoxazole and trimethoprim powder (SKG, Pharma Ltd, Germany), polyvinyl pyrrolidone (Merck, Germany), carboxymethylcellulose "Avicel" (Merck, Germany), corn starch (BDH. Chemicals U.K.), acacia gum (Myrton Jaunders and Co Ltd, Liverpool), benzoic acid B.P., amaranth solution (E. Merck Darmstadt, Germany), and sorbitol (E. Merck, Germany). Honey was purchased locally, while distilled water was obtained from the stock of Department of Pharmaceutics and Pharmaceutical Technology, Olabisi Onabanjo University, Sagamu.

Equipment and Apparatus

Equipment and other apparatus used were glass mortar and pestle (England), oven (Ketan, model 12016, India), beakers (Pyrex, England), viscometer (Brookfield

synchro-lectric viscometer, model L.V.F, Brookfield Engineering Laboratories, Stoughton Massachusetts), and Top loading balance (Phillips, weighmech PVT Ltd).

Preparation of co-trimoxazole suspension

A 50 g quantity of compound tragacanth powder, 0.8 g of trimethoprim, 4 g of sulphamethoxazole, and 0.1 g of banana flavour powder were accurately weighed and triturated in aliquot proportion in a glass mortar with 50 mls of honey which was added in bits to form a smooth paste. A 2 ml volume of benzoic acid solution and 0.2 mls of amaranth solution were added gradually with constant stirring. The mixture was then transferred into a calibrated amber bottle and was made up to 50 mls volume with distilled water. The mixture was vigorously shaken and well labeled. This procedure was repeated substituting the suspending agent in the formulation with polyvinyl pyrrolidone, corn starch, acacia gum, and carboxymethyl cellulose respectively. In all the above formulations, sorbitol was later used as control against honey as viscosity imparting medium. Five different brands of co-trimoxazole suspensions registered by National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria, were evaluated alongside the test formulations.

Determination of the sedimentation volume

A 50 ml volume of each suspension was stored undisturbed, in a 50 ml cylinder. The sedimentation volume of the suspension was then determined at room temperature, for one week. The measurement was taken hourly for 7 hours

and daily for 7 days. The suspension was then further observed for five weeks. The sedimentation volume (F) was calculated using the equation:

$$F = \frac{V_u}{V_o} \dots \text{Eqn. (2)}$$

Where V_u = final volume of sediment
 V_o = initial volume of sediment

Flow rate determination

The time to empty 10 mls of the suspension from a 10 ml pipette was calculated to give the flow rate which was computed thus:

$$\text{Flow rate} = \frac{\text{volume of pipette (mls)}}{\text{Time to empty the pipette (secs)}}$$

Rheology

Brookfield viscometer was used to measure the viscous traction on a spindle rotating in the liquid, contained in a beaker. The rate of shear was varied widely throughout the sample. All measurements were made in duplicates.

Statistical analysis

The data collected in this study were quantitative (continuous) in nature. Both descriptive and inferential approaches were used in analyzing the data. Two-way ANOVA, a parametric statistical application was used. Also, One-way student t-test was used where applicable. The probability level of significance by which conclusion was drawn was 5%.

RESULTS

The effects of the suspending agents and viscosity imparting agents on the sedimentation volume of the cotrimoxazole formulations are presented in Tables 1 – 3.

Table 1: Effects of suspending agents and viscosity imparting medium (Honey and sorbitol) on sedimentation volume of co-trimoxazole formulations as compared with brand products.

Brand products and	Sedimentation Volume														
	Time (hrs)								Time (days)						
	0	1	2	3	4	5	6	7	1	2	3	4	5	6	7
A	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
B	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.94	0.90	0.84	0.80	0.76	0.76
C	1.00	0.90	0.80	0.72	0.62	0.54	0.44	0.34	0.28	0.24	0.22	0.22	0.22	0.22	0.22
D	1.00	0.88	0.84	0.80	0.76	0.72	0.62	0.56	0.44	0.16	0.12	0.10	0.10	0.09	0.09
E	1.00	0.32	0.28	0.24	0.22	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
F ₁	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.96	0.92	0.88	0.84
F ₂	1.00	0.68	0.62	0.56	0.40	0.20	0.16	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.10
F ₃	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.94	0.92	0.90	0.90	0.84
F ₄	1.00	0.88	0.84	0.66	0.48	0.30	0.24	0.14	0.10	0.08	0.08	0.08	0.08	0.08	0.08
F ₅	1.00	0.62	0.50	0.42	0.28	0.24	0.16	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
F ₆	1.00	0.76	0.64	0.56	0.44	0.32	0.24	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
G ₁	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.96	0.90
G ₂	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.97	0.95	0.93	0.93	0.92
G ₃	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.96	0.94	0.92	0.90
G ₄	1.00	1.00	1.00	0.76	0.64	0.56	0.44	0.36	0.36	0.34	0.30	0.14	0.10	0.10	0.10
G ₅	1.00	0.72	0.44	0.30	0.20	0.14	0.12	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
G ₆	1.00	0.60	0.52	0.42	0.30	0.20	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10

Keys: F₁, F₂, F₃, F₄, F₅, F₆ represent formulations with suspending agents compound tragacanth B.P, polyvinyl pyrrolidone, corn starch, Acacia gum, carboxymethyl cellulose and control without suspending agent respectively in honey while G₁ to G₉ represent the formulations using sorbitol in place of honey for all the suspending agents listed above

Table 2: Effect of type of suspending agents and vehicle (Honey and Sorbitol) on flow rate (ml/sec) of co-trimoxazole suspensions.

Brand products and laboratory preparations	Serial number	Time (Secs)	Flow rate (ml/sec)
A	1	205	0.05
B	2	90	0.4
C	3	25	0.40
D	4	15	0.67
E	5	9	1.11
In honey			
F ₁	1	215	0.05
F ₂	2	115	0.09
F ₃	3	105	0.10
F ₄	4	110	0.09
F ₅	5	11	0.09
F ₆	6	10	1.00
In Sorbitol			
G ₁	1	220	0.05
G ₂	2	95	0.10
G ₃	3	80	0.13
G ₄	4	115	0.09
G ₅	5	12	0.83
G ₆	6	12	0.83

Table 3: Effect of type of suspending agents and vehicle (Honey and Sorbitol) on viscosity of co-trimoxazole suspensions

Brand products and laboratory preparations	Serial number	Viscosity (poise) at 25°C
A	1	5.95
B	2	2.45
C	3	2.25
D	4	2.10
E	5	0.10
In honey		
F ₁	1	6.25
F ₂	2	4.95
F ₃	3	3.10
F ₄	4	2.92
F ₅	5	2.25
F ₆	6	1.70
In Sorbitol		
G ₁	1	6.05
G ₂	2	5.10
G ₃	3	3.50
G ₄	4	3.30
G ₅	5	2.15
G ₆	6	1.15

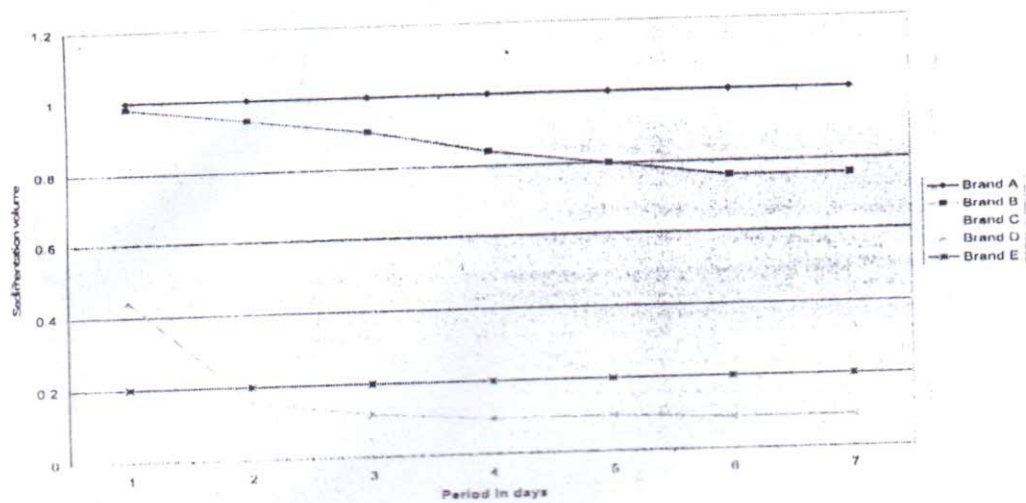


Fig 1: Sedimentation volume of commercial brands over a period of seven days

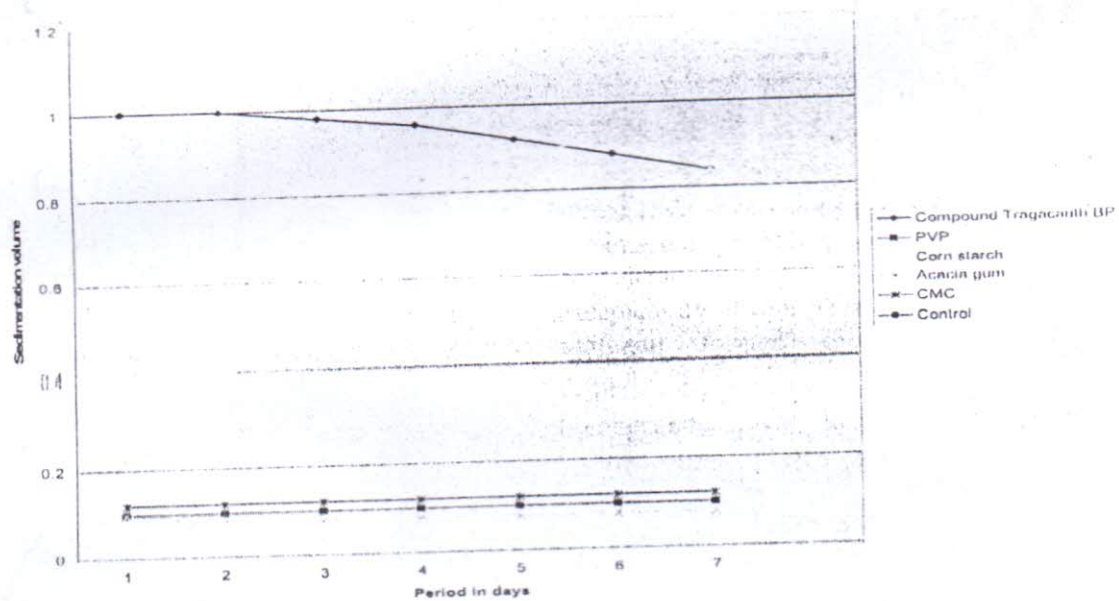


Fig 2: Sedimentation volume of co-trimoxazole formulations with different suspending agents in Honey

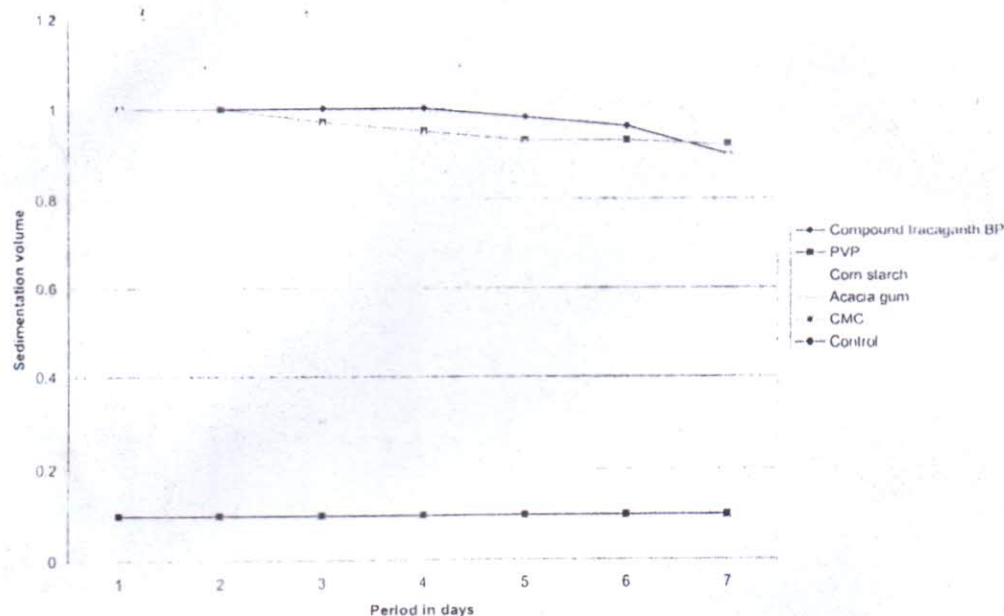


Fig 3: Sedimentation volume of co-trimoxazole formulations with different suspending agents in Honey

DISCUSSIONS

A knowledge of the theoretical considerations pertaining to suspension technology should ultimately help the formulator to select the ingredients that are most appropriate for the suspension and to use the available mixing and milling equipment to the best advantage (8).

Some of the commercially available brands of co-trimoxazole suspension have been associated with problem of rapid settling of the particulate ingredients, ultimately leading to caking and non-uniformity in doses during usage. The present work attempted to address this problem by altering the viscosity imparting vehicle and through the use of various suspending agents.

The effects of the type of suspending agents and viscosity imparting medium on sedimentation volume of co-

trimoxazole suspensions are shown in Fig. 1. Since redispersibility is one of the major considerations in assessing the acceptability of a suspension and since the sediment formed should be easily dispersed by moderate shaking to yield a homogenous system, measurement of the sedimentation volume and its ease of redispersion form two of the most common basic evaluative procedures (9).

The concept of sedimentation volume is simple. In short, it considers the ratio of the ultimate height (H_u) of the sediment to the initial height (H_0) of the total suspension as the suspension settles in a cylinder under standard conditions. The larger this fraction, the better is the suspendability.

According to Table 1 and Fig 1. Formulations A and B appear to have a high fraction of sedimentation volume among five commercial brands studied.

This shows a reliable suspendability. For the rest of the brands C,D and E tend to have a reduction in sedimentation volume fraction across the period of investigation. This probably indicates rapid settling of particulate matter in the suspension pointing to poor suspendability. One-way Anova statistical application to data obtained to ascertain statistical significance in the sedimentation volume fraction among the commercial brands studied or otherwise point towards rejection of null hypothesis. The conclusion therefore is that there is statistical significance in the sedimentation fraction $P < 0.05$ of all the commercial brands studied.

For the formulations in honey as viscosity imparting vehicle, batches F_1 and F_3 (formulations with compound Tragacanth and Corn starch as suspending agents respectively) tended to have higher sedimentation volume fraction relative to other formulations F_2 , F_4 , F_5 and F_6 (preparations with polyvinyl pyrrolidone, acacia gum, carboxy methylcellulose and control without suspending agent respectively) with lower sedimentation volume fraction across the period of study. The formulations in sorbitol and with compound Tragacanth, polyvinylpyrrolidone and Corn starch i.e. G_1 - G_3 appear to have favourable suspendability. Statistical application of Two-way Anova assessing the significance of effect of the two factors, viscosity and suspending ability of the suspending agent points to the fact that there is strong statistical significance in the effect of these factors on the suspendability of co-trimoxazole suspension at 95% confidence level.

From the data obtained as can be seen in Table 1, formulations in sorbitol appear to have better stability than formulations in honey as far as sedimentation volume fraction is concerned.

The flow rate is affected by the thickness or viscosity of the fluid and

viscosity depends on the materials used. The flow rate decreases as the viscosity of the medium increases and as a result, it will take a longer time for the preparation to pass through the orifice of the pipette. From Table 2, it was observed that the flow rate ranged from 0.05 ml/sec – 1.11 ml/sec for commercial samples A – E. The difference in the flow rate of formulations may be as a result of the type and amount of ingredients used in the formulation especially the suspending agents and the viscosity imparting medium which have different inherent effect and quality on suspensions formulated.

The flow rate results for the formulations in honey and sorbitol appear to be fluctuating across the samples studied. The data obtained appear to be in agreement with the null hypothesis of no statistical significance in the flow rate of the samples studied $p < 0.05$ for both honey and sorbitol using student t-test (unpaired, two-tailed) statistical tool.

CONCLUSION

From the foregoing, it appears that formulations with sorbitol using compound tragacanth, corn starch, polyvinylpyrrolidone as suspending agents have better suspendability indices than that of honey with compound tragacanth, corn starch as suspending agents. In addition, some of the test formulations compared favorably well with the commercial brands.

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