Artículo de investigación clínica / *http://dx.doi.org/10.15446/rcciquifa.v49n3.91344*

Conocimiento preventivo y su práctica entre la población de Colombia hacia la enfermedad por Coronavirus (COVID-19): una perspectiva de género

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Recibido: 13 de julio de 2020

Revisado: 24 de julio de 2020

Aceptado: 27 de julio 2020

Resumen

Este estudio investiga el conocimiento existente de la COVID-19 en ambos sexos y propone una práctica para prevenir la COVID-19. Se realizó un estudio transversal con una encuesta en línea recopilando datos en diferentes regiones de Colombia, a través de un cuestionario validado estructurado y de diseño propio basado en el asesoramiento público general de la Organización Mundial de la Salud (OMS) sobre la prevención de la COVID-19. Este estudio ha empleado la técnica de muestreo de bola de nieve, y contó con 445 participantes (46,5% hombres y 53,5% mujeres). Se identificó que las mujeres no solo tienen un mejor conocimiento, sino que su comportamiento en la práctica es mucho mejor que sus contrapartes masculinas. Aunque los resultados entre hombres y mujeres son muy similares, la pregunta de quedarse en casa es bastante concluyente a favor de las mujeres, quienes son más responsables. Finalmente, el estudio demuestra que las mujeres corren menos riesgo en comparación con los hombres, porque estas tienen mejores prácticas de prevención, como lo indican las estadísticas. Este estudio destaca aún más la idea de que las mujeres son menos propicias para contraer la infección de covid-19 debido a su mejor comportamiento de práctica que los hombres.

Palabras clave: COVID-19, conocimiento preventivo, práctica, Colombia, género, coronavirus.

Summary

Preventive knowledge and its practice among Colombian population towards coronavirus disease (COVID-19): A Gender-Based Perspective

This study investigates the existing knowledge of covid-19 among both genders and a likely use of it in practice to combat COVID-19. Cross sectional study with an online survey and data was collected from Colombia, through a structured, self-design validated questionnaire was created based on the World Health Organization (WHO) general public advice towards COVID-19 prevention. This study has employed snow-ball sampling technique, counted on 445 participants (46.5% male and 53.5% female). This study has found out that women not only carry better knowledge, but their practicing behavior is far better than their male counterparts. Although the results between men and women are very similar, the question about staying at home is quite conclusive in favor of women, who are more responsible. Finally his study proves that women are on a less risk in comparison to men on the basis of prevention practices exercised better as the prevailing statistics indicate. This study highlighted the notion further that women are less conducive to infection of COVID-19 due to their better practicing behavior than men.

Key words: COVID-19, preventive knowledge, practice, Colombia, gender based, coronavirus.

Introducción

El coronavirus SARS-CoV-2, es un nuevo virus zoonótico de la familia coronaviridae que genera la enfermedad por coronavirus 2019 (COVID-19), este virus fue detectado por primera vez en diciembre de 2019 en la ciudad de Wuhan (China) [1], y desde entonces hasta la fecha se han registrado 12 476 028 casos de personas contagiadas en el mundo y 559 998 muertes a causa del mismo, así el coronavirus 2019 en una amenaza importante para la salud pública mundial [2]. La Organización Mundial de la Salud (OMS) lo declara pandemia el 11 de marzo de 2020 y estableció que el coronavirus 2019 causa infecciones respiratorias que pueden ir desde un resfriado común, hasta enfermedades más graves como el síndrome respiratorio agudo grave. Los síntomas de esta patología se han relacionado con los generados por el síndrome respiratorio agudo severo (SARS) y con el síndrome respiratorio del oriente medio (MERS) [3], enfermedades respiratorias causadas por especies de Coronavirus que se transmiten de

persona a persona. Debido a que cuenta con un nivel alto de propagación la OMS hace un llamamiento a todos los países en acoger medidas preventivas urgentes y agresivas ante la pandemia [4].

Desde entonces organizaciones gubernamentales y no gubernamentales han iniciado e incentivado la investigación científica desde diferentes enfoques, pero con un único objetivo: desarrollar la solución que contrarreste la pandemia. La comunidad científica ha generado diversos estudios que han proporcionado información importante, la cual ha permitido identificar las variables directas e indirectas en la propagación del virus, además de avanzar en el desarrollo de un tratamiento antiviral efectivo o una vacuna [5]. Esta solución aún está lejana, por ello, actualmente, varios países han adoptado medidas preventivas que permitan disminuir los contagios por COVID-19 de persona a persona. En Colombia se ha acogido la técnica preventiva basada en el conocimiento y la importancia de la práctica de medidas de prevención como el uso de mascarilla, lavado frecuente de las manos y mantener el distanciamiento social, medidas preventivas recomendadas por organizaciones como el Centros para el Control y la Prevención de Enfermedades [6], la Organización Mundial de la Salud [4] y el Ministerio de Salud de Colombia [7], entre otras.

De acuerdo con la Asociación Europea de Editores de Ciencia, la editorial de la revista *The Lancet* y *GlobalHealth50/50* es necesario investigar las enfermedades desde la perspectiva de género, debido a que en brotes pasados como el SARS, MERS, ébola, zika, se ha evidenciado la mortalidad en hombres y la vulnerabilidad de la enfermedad en mujeres [8]. Los expertos coinciden que es necesario contar con información más detallada que incluyan variables como sexo y edad para generar estrategias que aporten al mejoramiento de atención primaria y secundaria en emergencias sanitarias por brotes. Según López [9] "La experiencia de brotes pasados muestra la importancia de incorporar un análisis de género en los esfuerzos de preparación y respuesta para mejorar la efectividad de las intervenciones de salud y promover objetivos de equidad de género y salud", a su vez, según la información suministrada por algunos entes, se identifica que actualmente la COVID-19 registra mayor mortalidad en hombres, debido a hábitos no saludables como el tabaquismo, la ingesta de bebidas alcohólicas, que propenden a que los hombres sufran de hipertensión, enfermedades cardiovasculares y enfermedades respiratorias lo cual aumenta la probabilidad de mortalidad en el mismo, por otro lado aunque no se establece qué género es el más vulnerable ante la COVID-19 [10], estudios relacionados entre conocimiento y aplicación de este, evidencian que las personas con un conocimiento claro y amplio sobre enfermedades, ejecutan prácticas adecuadas. Generalmente, las mujeres están más informadas y adoptan comportamientos más favorables, que ayudan a la prevención de enfermedades [11].

Metodología

Este un estudio observacional cuantitativo de corte trasversal basado en encuestas diligenciadas en internet. Los datos para este estudio se obtuvieron de 17 departamentos de Colombia: Antioquia, Atlántico, Boyacá, Caldas, Caquetá, Cauca, Cundinamarca, Huila, Magdalena, Meta, Quindío, Risaralda, Santander, Sucre, Tolima y Valle del Cauca y Bogotá D.C., utilizado la técnica de muestreo de bola de nieve no probabilístico.

Se desarrolló un cuestionario para el público basado en la recomendaciones de la Organización Mundial de la Salud [4], estipulando medidas preventivas básicas contra el COVID-19 como lavarse las manos frecuentemente, adoptar medidas de higiene respiratoria, mantener un distanciamiento social de mínimo un metro, cuidados al toser, permanecer en los hogares, entre otras.

La herramienta de recolección de datos esta divida en tres partes. La primera estaba relacionada con la información sociodemográfica como sexo, edad, formación académica y estrato socioeconómico. La segunda parte contenía preguntas relacionadas con el conocimiento de la prevención de COVID-19 y su práctica en la vida cotidiana; este apartado está constituido por un total de 14 preguntas, de las cuales 7 eran para conocimiento y otras 7 para medir la apropiación de ese conocimiento en la vida cotidiana. La última parte del cuestionario contiene 7 preguntas basadas en el conocimiento de la persona, relacionado con la protección contra COVID-19 de acuerdo con las recomendaciones de la OMS. Estas preguntas están relacionadas con el tiempo de cuarentena de personas que llegan del extranjero y las llamadas al número de emergencia 192 en caso de síntomas relacionadas con la infección.

Todas las respuestas se registraron como "Sí" o "No". Los datos se recopilaron mediante un formulario en línea de Google Drive®. El objetivo del estudio se describió a los encuestados antes del consentimiento y la participación fue completamente voluntaria. Se registraron un total de 445 respuestas (considerando una población de 50 100 000 habitantes y, de acuerdo con los parámetros de la fórmula para calcular el tamaño de la muestra sobre una población finita, con un nivel de confianza del 95 % se establece un numero de muestra de 383). Los datos fueron recopilados desde el 8 hasta el 10 de julio de 2020. Todos los datos se codificaron y transfirieron a Microsoft Excel®, y luego se transfirieron a el programa RStudio versión libre para su análisis. Se utilizó la prueba de chi-cuadrado de Pearson para verificar la significación estadística. El valor de $p < 0{,}05$ se consideró significativo.

Resultados y discusión

Se encuestaron a un total de 445 personas (hombres: 46,5%; mujeres: 53,5%), los rangos de edad se establecieron de acuerdo con ciclo propuesto por el Ministerios de Salud [12] que define que el 18% son jóvenes de entre 18 y 26 años de edad, el 77,1% son personas adultas de entre 27 y 59 años de edad y el 4,9% son mayores de edad (>60 años). En cuanto a la formación académica la mayor proporción son profesionales (49,7) seguido de profesionales con maestría (24%) y educación media (20,2). Finalmente, en cuanto a información sociodemográfica, la población encuestada en su mayoría pertenece a los estratos 2 y 3 (41,8% y 31,5%) (tabla 1).

Tabla 1. Información sociodemográfica de la población encuestada.

Variables	Masculino (n= 207; 46,5%)	Femenino (n=238; 53,5%)	Total (n =445)
	n (%)	n (%)	n (%)
Edad en años			
18-26	31 (7,0)	49 (11,0)	80 (18,0)
27-59	164 (36,9)	179 (40,2)	343 (77,1)
>60	12 (2,7)	10 (2,2)	22 (4,9)
Formación académica			
Primaria	4 (0,9)	4 (0,9)	8 (1,8)
Secundaria	32 (7,2)	58 (13,0)	90 (20,2)
Profesional	100 (22,3)	121 (27,2)	221 (49,7)
Maestría	60 (13,5)	47 (10,6)	107 (24)
Doctorado	11 (2,5)	8 (1,8)	19 (4,3)
Estrato socioeconómico			
1	6 (1,3)	25 (5,6)	31 (7,0)
2	94 (21,1)	92 (20,7)	186 (41,8)
3	69 (15,5)	71 (16,0)	140 (31,5)
4	28 (6,3)	33 (7,4)	61 (13,7)
5	8 (1,8)	11 (2,5)	19 (4,3)
6	2 (0,4)	6 (1,4)	8 (1,8)

En general, la población está informada y respondió de manera correcta las preguntas basadas en el conocimiento relacionadas con la propagación de COVID-19, incluido, el uso de mascarilla o tapabocas (P1. 96,9%) lavarse las manos durante 20 segundos (P2. 96,6%), estornudar o toser en el brazo/codo (P3. 85,9%) , el coronavirus se puede transferir dándose la mano (P4. 90,8%), manteniendo una distancia segura de al menos 1 metro (88,1%), tocando la cara puede transferir el coronavirus (P5. 95,1%), quedarse en casa puede disminuir las posibilidades de contraer una infección (P6. 98,0%). Los encuestados informaron el menor conocimiento acerca de la pregunta que refiere que el coronavirus puede permanecer en los objetos durante algunas semanas o días (P10. 83,6%) y de la llamada al 192 para buscar atención médica para el coronavirus (P8. 79,5%). Pese a que los porcentajes sobre aciertos en general son altos, preguntas como la P1, P3 y P4 que implican interacción social, presentan entre el 4% al 15 % de desconocimiento, lo que pone en alto riesgo la población.

Realizado un análisis en función del género (tablas 2 y 3), los resultados muestran lo siguiente: con respecto al "uso de mascarilla o tapabocas (P1)", las mujeres tienen un mejor conocimiento respecto a los hombres (F: 98%; M: 96%; p>0,05). En respuesta al "lavado de manos durante mínimo 20 segundo (P2)", de nuevo las mujeres muestran tener un mejor conocimiento respecto a los hombres (F: 98%; M: 95%; p>0,05). En respuesta al conocimiento sobre "estornudar o toser en el brazo / codo (P3)", las mujeres estaban mejor informadas que los hombres y el valor "p" fue estadísticamente significativo (F: 92%; M: 79%; p<0,05), indicando una relación entre la respuesta y el género. Frente al conocimiento "sobre el contagio de COVID-19 por darse la mano (P4)" las mujeres presentaron mayores aciertos (F: 93%; M: 88%; p>0,05). A la pregunta sobre "distanciamiento social (P5)" las mujeres muestran un mejor conocimiento que los hombres (F: 90%; M: 86%; p>0,05). En cuanto a la pregunta sobre "tocar la cara puede transferir el coronavirus (P6)" las mujeres continúan estando mejor informadas que los hombres (F: 97%; M: 93%; p>0,05). El conocimiento sobre "quedarse en casa puede disminuir las posibilidades de contraer una infección (P7)", (F: 98%; M: 99%; p>0,05) ambos géneros son conscientes del tema con un leve repunte en los hombres. En respuesta a la pregunta sobre "puede llamar al 192 para buscar atención médica para el coronavirus (P8)", de nuevo además de no haber una diferencia marcada entre géneros ambos presentan un buen conocimiento sobre la línea telefónica (F: 79%; M: 80%; p>0,05). El conocimiento sobre "las personas mayores tienen un mayor riesgo de desarrollar coronavirus (P9) "continua la similitud en las respuestas entre hombres y mujeres (F: 98%; M: 97%; p>0,05). En respuesta a "el coronavirus puede permanecer en los objetos durante algunas semanas o días (P10)", ambos sexos, ofrecen respuestas similares (F: 84%; M: 83%; p>0,05). Del mismo modo, para la pregunta "las personas que han viajado desde el extranjero no deben conocer a otras personas durante 2

semanas (P11)", la respuesta de ambos sexos es prácticamente la misma (F: 100%; M: 99%; p>0,05), y es la pregunta de mayor acierto por parte de los encuestados. Respondiendo a "evitar el contacto con personas que tienen tos/fiebre (P12)", vuelve a presentarse el consenso entre hombres y mujeres, con un alto grado de acierto de todas las personas (F: 99%; M: 98%; p>0,05). En respuesta a la pregunta "debe buscar atención médica si tiene tos, fiebre y dificultad para respirar (P13)" la tendencia es la misma entre sexos (F: 98%; M: 97%; p>0,05).

Tabla 2. Preguntas sobre el conocimiento de algunas medidas preventivas contra la COVID-19, propuestas por la OMS.

P	Pregunta		Masculino n (%)	Femenino n (%)	Total n (%)	Valor-p
1	¿El uso de mascarilla o tapaboca ayuda a prevenir el contagio de coronavirus?	Sí	198 (95,6)	233 (97,9)	431 (96,9)	0,2792
		No	9 (4,3)	5 (2,1)	14 (3,1)	
2	¿Lavarse las manos durante 20 segundos, puede ayudar a prevenir el coronavirus?	Sí	196 (94,7)	234 (98,3)	430 (96,6)	0,0636
		No	11 (5,3)	4 (1,7)	15 (3,4)	
3	¿Toser o estornudar en el brazo/ codo puede evitar la propagación del coronavirus?	Sí	164 (79,2)	218 (91,6)	382 (85,9)	**0,0003**
		No	43 (20,8)	20 (8.4)	63 (14.1)	
4	¿El coronavirus puede transferirse por darse la mano?	Sí	183(88.4)	221(92,8)	404 (90,8)	0,1456
		No	24 (11,6)	17 (7,2)	41 (9,2)	
5	¿Mantener una distancia mínima de 1 metro con otras personas ayuda al no contagio del coronavirus?	Sí	177 (85,5)	215 (90,3)	392 (88,1)	0,155
		No	30 (14,5)	23 (9,7)	53 (11,9)	
6	¿Tocarse la cara puede transferir el coronavirus?	Sí	193(93,2)	230 (96,6)	423 (95,1)	0,1521
		No	14 (6,8)	8 (3,4)	22 (4,9)	
7	¿Permanecer en cuarentena (estar en casa) disminuye la probabilidad de contraer el coronavirus?	Sí	204(98,6)	232 (97,5)	436 (98,0)	0,643
		No	3 (1,4)	6 (2,5)	9 (2,0)	
8	¿El gobierno nacional dispone de la línea gratuita 192 para orientación sobre COVID-19?	Sí	166(80,2)	188 (79,0)	354 (79.5)	0,8449
		No	41 (19,8)	50 (21,0)	91 (20,4)	
9	¿Las personas de la tercera edad son más vulnerables ante el COVID-19?	Sí	201(97,1)	234 (98,3)	435 (97,8)	0,5865
		No	6 (2,9)	4 (1,7)	10 (2,2)	

(*Continúa*)

Tabla 2. Preguntas sobre el conocimiento de algunas medidas preventivas contra la COVID-19, propuestas por la OMS.

P	Pregunta		Masculino n (%)	Femenino n (%)	Total n (%)	Valor-p
10	¿El virus puede permanecer en los objetos durante días o semanas?	Sí	171(82,6)	201 (84,4)	372 (83,6)	0,6922
		No	36 (17,4)	37 (15,6)	73 (16,4)	
11	¿Las personas que llegan del extranjero deben permanecer aisladas durante un periodo mínimo de 14 días?	Sí	205(99,0)	237 (99,6)	442 (99,4)	0,9034
		No	2 (1,0)	1 (0,4)	3 (0,6)	
12	¿Se debe evitar el contacto con personas que presentan tos o fiebre?	Sí	203 (98,1)	236 (99,2)	439 (98,6)	0,5591
		No	4 (1,9)	2 (0,8)	6 (1,3)	
13	¿Se debe buscar atención médica si se presentan síntomas de tos, fiebre, problemas para respirar?	Sí	201 (97,1)	234 (98,3)	435 (97,8)	0,5865
		No	6 (2,9)	4 (1,7)	10 (2,2)	

Tabla 3. Preguntas sobre la práctica de algunas medidas preventivas contra la COVID-19, propuestas por la OMS.

P	Pregunta		Masculino n (%)	Femenino (%)	Total n (%)	Valor-p
14	¿Usted utiliza siempre mascarilla o tapaboca al salir de su casa?	Sí	203 (98,1)	235 (98,7)	438 (98,4)	0,8523
		No	4 (1,9)	3 (1,3)	7 (1,6)	
15	¿Usted lava sus manos frecuentemente y mínimo por 20 segundos?	Sí	182 (87,9)	217 (91,2)	399 (89,7)	0,3328
		No	25 (12,1)	21 (8,8)	46 (10,3)	
16	¿Usted se cubre la cara con el brazo/codo al toser o estornudar?	Sí	183 (88,4)	219 (92,1)	402 (90,3)	0,2605
		No	24 (11,6)	19 (7,9)	43 (9,7)	
17	¿Usted al saludar a otra persona da la mano o beso?	Sí	20 (9,7)	22 (9,2)	42 (9,4)	1,0
		No	187 (90,3)	216 (90,8)	403 (90,5)	
18	¿Usted mantiene una distancia mínima de 1 metro mientras se encuentra con otras personas en estos días de pandemia?	Sí	183 (88,4)	228 (95,8)	411 (92.3)	**0,0060**
		No	24 (11,6)	10 (4,2)	34 (7,6)	

(*Continued*)

Tabla 3. Preguntas sobre la práctica de algunas medidas preventivas contra la COVID-19, propuestas por la OMS.

P	Pregunta		Masculino n (%)	Femenino (%)	Total n (%)	Valor-p
19	¿Usted evita tocarse la cara?	Sí	180 (87,0)	221 (92,8)	401 (90,1)	0,0548
		No	27 (13,0)	17 (7,2)	44 (9,9)	
20	¿Usted permanece en casa a menudo?	Sí	181 (87,4)	219 (92,0)	400 (89,9)	0,1499
		No	26 (12,6)	19 (8,0)	45 (10,1)	

En cuanto a las respuestas sobre preguntas que pretenden evaluar la apropiación del conocimiento (P14-P20) (tabla 3) la práctica de usar mascarilla o tapabocas (P14) y saludar a personas dándoles la mano o un beso (P17), no hay diferencia significativa entre las respuestas dadas por hombres y mujeres. Aunque P14 presenta un grado de apropiación, P17 muestra que un 10% de las personas continúan saludando, dando la mano/beso, lo que se constituye en un factor de riego alto para la propagación de la pandemia. En cuanto a lavase las manos por mínimo 20 segundos (P15), las mujeres practicaban más esta acción que los hombres (F: 91%; M: 88%; $p>0,05$). Respeto a cubrirse la cara con el codo/brazo al estornudar o toser, de nuevo las mujeres son más consientes al realizar esta práctica (F: 92%; M: 88%; $p>0,05$). Al indagar sobre el distanciamiento social de mínimo 1 metro, las mujeres practican más esta acción que los hombres y presenta un p menor a 0,05 indicando una relación entre el sexo del individuo y la práctica (F: 96%; M: 88%; $p<0,05$); finalmente, a las preguntas "evita tocarse la cara (P19)" y "permanece en casa a menudo (P20)" las mujeres vuelven a tener un mayor grado de concienciación (F: 93%; M: 87%; $p<0,05$) y (F: 92%; M: 87%; $p<0,05$).

En la tabla 4 se presentan los porcentajes de aplicación del conocimiento en la práctica, y se identificó un fenómeno que, aunque no se podría calificar como atípico, puede llegar a ser interesante. Si bien las personas registran no tener conocimiento sobre una práctica, sus acciones son correctas, por lo que se obtienen porcentajes mayores al 100% como es el caso de las relaciones (R) 1, 3, 4 y 5. Lo anterior, podría deberse a que, si bien las personas no tienen el conocimiento, o creen que estas prácticas no contribuyen al control de la pandemia, la obligación de cumplir una norma jurídica o social obliga a los individuos a actuar de forma correcta.

Ahora bien, con respecto al uso de mascarillas (R1) o tapabocas los hombres practican más sus conocimientos que las mujeres (102,5 vs. 100,9), los hombres también practican más sus conocimientos respecto a poner su brazo o codo al estornudar (R3) (111,6 vs 100,4) y no estrechar la mano o dar besos (R4) (102,2 vs 97,7). Con relación a

Tabla 4. Apropiación del conocimiento relacionado con prácticas recomendadas por la OMS para contrarrestar la pandemia de la COVID-19.

R	Apropiación del conocimiento	Masculino %	Femenino %	Valor-p
1.	Influencia del conocimiento del uso de la mascarilla o tapaboca al salir de su casa	102,5	100,9	0,9582
2.	Influencia del conocimiento de lavarse las manos en la práctica	92,9	92,7	0,9519
3.	Influencia del conocimiento de estornudos/ tos en la práctica	111,6	100,4	0,5105
4.	Influencia del conocimiento de no estrechar la mano en la práctica	102,2	97,7	0,8070
5.	Influencia del conocimiento de la distancia social en la práctica	103,4	106,0	0,9142
6.	Influencia del conocimiento sobre la propagación de la infección al tocar la cara en la práctica	93,26	96.01	0,8864
7.	Influencia del conocimiento de quedarse en casa para prevenir infecciones en la práctica	88,7	94,39	0,7065

practicar su conocimiento del lavado de manos durante al menos 20 minutos (R2) tanto hombres como mujeres presentan una apropiación del 93%. En cuanto a las relaciones 5 (distanciamiento social), 6 (tocarse la cara) y 7 (permanecer en casa), las mujeres adoptaron más estas prácticas que los hombres.

El objetivo del presente estudio fue medir las diferencias específicas de género en el conocimiento y la práctica para prevenir COVID-19 en la población colombiana. Actualmente, no hay una vacuna contra este virus y las opciones de tratamiento no tienen respuesta efectiva. Las organizaciones mundiales de salud pública, incluida la OMS [4], los ministerios de salud de diferentes países y el Centro para el Control y la Prevención de Enfermedades de Estados Unidos [13] han recomendado al público adoptar medidas preventivas simples para limitar la exposición y la propagación del virus. Estas recomendaciones son prácticas de higiene, aislamiento y distanciamiento social como la forma más efectiva de detener la propagación del virus. El Ministerio de Salud de Colombia ha implementado programas de sensibilización pública y medidas de prevención y mitigación. Estos programas contribuyeron con un papel integral para concienciar al público sobre los síntomas, la propagación y las recomendaciones para la prevención mediante diferentes medios de comunicación.

En general, este estudio reveló que la mayoría de los encuestados tenían un nivel significativo de conocimiento y también seguían las instrucciones de prevención recomendadas

por la OMS. Sin embargo, las mujeres están mejor informadas sobre las preguntas basadas en el conocimiento y también asimilaban mejor los conocimientos relacionados con la prevención del virus en comparación con los hombres. La significativa apropiación del conocimiento (tabla 4) puede ser consecuencia de varios factores como, el impacto de las campañas de sensibilización, la exigencia en la aplicación de normas tendientes al control de la pandemia, entre otros. Esto muestra, que las mayorías de las personas presentan un alto grado de sensibilización, además de permanecer bien informadas pese al gran número de noticias falsas presentadas en redes sociales [14,15] que pueden llevar a la población a automedicarse, esto podría implicar mayores complicaciones en los sistemas de salud [16, 17].

Otro hallazgo interesante de este estudio es que las mujeres también presentaban una mayor aplicación de sus conocimientos en comparación con sus homólogos masculinos. La mortalidad e infección por COVID-19 entre hombres es mayor en comparación con las mujeres. Los datos de los 39 países más afectados no presentan un informe contúndete sobre quien padece más la infección entre hombres y mujeres, sin embargo, la mortalidad de los hombres es mayor en comparación con las mujeres [18]. Los resultados adversos en los hombres están relacionados con comorbilidades, que incluyen enfermedades pulmonares, hipertensión y problemas cardiovasculares, que están relacionados con el tabaquismo y el consumo de alcohol, en comparación con las mujeres (4,7% frente a 2,8%) [19]. Estudios anteriores sobre el SARS, la gripe, el ébola y el VIH han mostrado diferentes relaciones entre la infección, hombres y mujeres, demostrando que los hombres corren mayor riesgo de infección [18].

La falta de conocimiento y prácticas para prevenir la COVID-19, sumado a la tendencia presentada por los estudios desarrollados por De Loyola Filho *et al*, y Ortiz *et al*, en Brasil y Colombia respectivamente [16, 20], los cuales documentan que los hombres presentan mayor tendencia por prácticas riesgosas como la automedicación, aumentan el riesgo de contagio. Como se constata en las últimas recomendaciones de funcionarios como el presidente de los Estados Unidos, Donald Trump y el alcalde la Ciudad de Santiago de Cali, sobre consumo de hidroxicloroquina, ivermectina y desinfectantes, además del uso del dióxido de cloro [21, 22]. Estas prácticas pueden transformarse en otro factor de riesgo que podría sumarse a la razón por la cual se presenta un mayor potencial de tasa de muertes entre los hombres, por lo que una mayor concienciación hacia los hombres podría disminuir la mortalidad de los mismos. Así mismo, estos estudios sustentan la mayor responsabilidad por parte de las mujeres frente al cuidado de su salud, lo que concuerda con los resultados obtenidos en el presente estudio.

Conclusiones

A partir de los hallazgos se puede observar que las mujeres no solo poseen un mejor conocimiento que los hombres para la mayoría de los ítems, sino que también aplican mejor las medidas prácticas que ellos. Las mujeres que se quedan en casa están menos expuestas al virus en comparación con los hombres, lo que puede ser un argumento de consideración válida para futuros estudios. En general, este estudio es un esfuerzo por contribuir con la comprensión de la noción de por qué los hombres son más propensos para la infección que las mujeres. Además, este estudio, aunque con todas sus limitaciones de solo enfocarse en la población colombiana es una contribución sustancial para que los responsables de políticas públicas lo incluyan como una guía en la emisión de medidas prácticas basadas en el conocimiento con perspectiva de género en la prevención la infección de COVID-19.

Conflicto de intereses

Los autores no declaran conflicto de intereses.

Agradecimientos

Nos gustaría expresar nuestro agradecimiento al señor Milcíades Ortiz D. por su colaboración en la recolección de la información para la presente investigación.

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Como citar este artículo

P.A. Rivera-Diaz, H. Rubiano-Daza, J.C. Quintero-Quimbaya, D.P. Hoyos-Armero, C. Herrera-Ramírez, S.M. Rivera-Ospitia, C.P. Ortiz, Conocimiento preventivo y su práctica entre la población de Colombia hacia la enfermedad por Coronavirus (COVID-19): una perspectiva de género, *Rev. Colomb. Cienc. Quím. Farm.*, **49**(3), 776-789 (2020).

Technological research article / *http://dx.doi.org/10.15446/rcciquifa.v49n3.91345*

Aloe gel: manipulation and characterization of physical-chemical quality adjustment

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Received: 14 July 2019

Revised: 24 July 2020

Accepted: 27 July 2020

Summary

The objective of the study was to develop and characterize the gel based on *Aloe vera* for the Manoel Casado de Almeida Pharmacy School. The research was done at the Education and Health Center off the Federal University of Campina Grande, located in the city of Cuité (PB). For the quality control, chemical physical tests were carried out as determine pH, apparent density, viscosity, spreadability and centrifugation test. The gel demonstrated acceptable physicochemical characteristics exhibiting pH 5, bulk density 0.1018 (± 0.0008), viscosity above 10 000 cP, and adequate stability. Complementary studies on microbiological quality are suggested, to give safety on their therapeutic potential in wound management.

Key words: *Aloe*, phytotherapy, medicinal plants, complementary therapies.

Resumen

Gel de aloe: manipulación y caracterización del ajuste de la calidad físico-química

El estudio tuvo como objetivo desarrollar y caracterizar el gel a base de *Aloe vera* para la Escuela de Farmacia Manoel Casado de Almeida. La investigación se llevó a cabo en el Centro de Educación y Salud, Universidad Federal de Campina Grande, ubicada en la ciudad de Cuité (PB). Para el control de calidad, se realizaron las siguientes pruebas físico-químicas: determinación de pH, densidad aparente, viscosidad, capacidad de propagación y prueba de centrifugación. El gel mostró características fisicoquímicas aceptables, con pH 5, densidad aparente 0,1018 (± 0,0008), viscosidad superior a 10 000 cP y estabilidad adecuada. Por lo tanto, se sugieren estudios complementarios con respecto a la calidad microbiológica, lo que garantiza la seguridad dado su potencial terapéutico en el tratamiento de heridas.

Palabras clave: *Aloe*, fitoterapia, plantas medicinales, terapias complementarias.

Resumo

Gel de babosa: manipulação e caracterização de parâmetros físico-químicos de qualidade

O estudo teve como objetivo desenvolver e caracterizar o gel a base de *Aloe vera* para Farmácia Escola Manoel Casado de Almeida. A pesquisa foi realizada no Centro de Educação e Saúde, da Universidade Federal de Campina Grande, situado na cidade de Cuité (PB). Para o controle de qualidade foram realizados os seguintes ensaios físico-químicos: determinação de pH, densidade aparente, viscosidade, espalhabilidade e teste de centrifugação. O gel demonstrou características físico-químicas aceitáveis apresentando pH 5, densidade aparente 0,1018 (± 0,0008), viscosidade acima de 10 000 cP e estabilidade adequada. Assim, sugere-se estudos complementares no tocante a qualidade microbiológica, garantindo a segurança dado seu potencial terapêutico no manejo de feridas.

Palavras-chave: *Aloe*; fitoterapia; plantas medicinais; terapias complementarias.

Introduction

Phytotherapy is an ancient practice that uses plants to treat diseases, being an alternative that does not use isolated active substances, preserving the original composition of the original plant [1, 2]. It is still possible to notice a certain resistance from prescribing professionals to the use of medicinal plants and herbal medicines. This low adherence occurs, often, due to the discredit in therapy and the lack of technical-scientific knowledge [3, 4].

Due to the high consumption of medicinal plants/herbal medicines and insecurity about their quality controls, on June 22, 2006, the National Policy on Medicinal Plants and Herbal Medicines [5] was created in Brazil, through a decree of the presidential republic. This measure is of great importance for SUS, which aims in its guidelines to ensure the effectiveness, quality and safety of these products, in addition to easy access for treatment. It is also the aim of SUS that these treatments be a less costly alternative, especially for poor communities.

Currently, the phytotherapy is experiencing a new level with recent publications, bringing credibility and security to patients and health professionals. Thus, transforming it not only in an alternative therapy, but in a possibility that the herbal medicines, in some cases, are considered as treatment of first choice [4].

Skin lesions, burns, skin infections and chronic wounds, have a greater difficulty in healing, impair the functions of the skin, and in more severe cases can lead to death. Thus, they require greater care in the long term, increasing costs for health systems worldwide [6].

In order to minimize costs, the use of medicinal plants and natural products is being a new alternative for the treatment of wounds, especially in developing countries [7]. The search for alternative therapies to promote wound healing has been intensified, while modern therapies with antibiotics and corticosteroids have been neglected due to the side effects that conventional drugs can cause [8].

Aloe vera L. or *Aloe barbadensis*, popularly known as "babosa", is one of the most important medicinal plants in the treatment of wounds, considering that countless studies report its healing and anti-inflammatory properties [9].

Considering the high consumption of medicinal plants and natural products as low-cost treatments by the low-income population, and understanding that the lack of uniformity of the chemical composition, together with the presence of contaminants, cause deficiency in the safety of these products, it is important to develop formulations

that ensure the quality of medicinal products of plant origin, since it directly interferes with efficacy and may offer risks to consumer health.

In this context, the present study aimed to develop and characterize a formulation of aloe gel as an alternative for the treatment of wounds, as well as to compose the portfolio of formulations of the Pharmacy School Manuel Casado de Almeida of the Federal University of Campina Grande, Education Center and Health, Campus Cuité (PB).

Material and methods

The research was carried out at the Federal University of Campina Grande, campus Cuité (CES), in the teaching laboratories of the Pharmacy course and in the Pharmacy School Manoel Casado de Almeida.

Plant material

Initially, *Aloe vera* leaves were collected from the medicinal plant garden at the Education and Health Center (CES), and then the material was prepared, which included: washing, removing mucilage and crushing to prepare the glycolic extract.

Preparation of glycolic extract

The extract was prepared according to the steps shown in figure 1. After crushing, the material was weighed and added in a wide-mouthed bottle. Separately, in a beaker, a solution of 50% Ethanol and 5% Propylene Glycol was prepared, and then added to the flask containing the mucilage, which was left to soak for eight days with daily stirring. After this period, the material was filtered, stored in amber glass, in a dry place and protected from light [10].

Preparation of *Aloe vera* gel

Table 1 shows the components present in the formulation of the *Aloe vera* gel, with their respective quantities specified for 100 g.

To produce the *Aloe vera* gel, the carbopol 940 gel shown in figure 2 was prepared.

Chemical physical analysis

pH determination

The pH was determined directly in a calibrated pH meter, as described in the Brazilian Pharmacopeia [12].

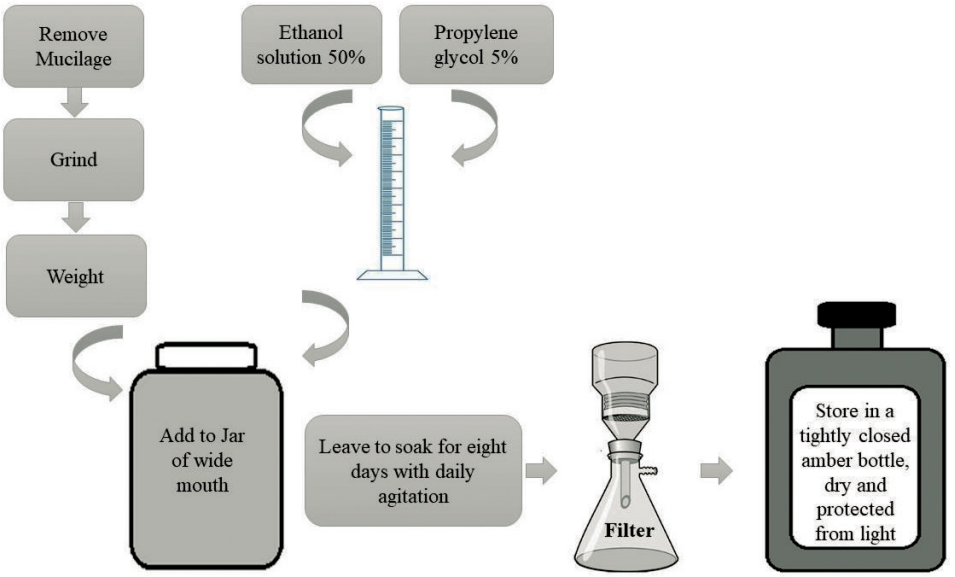

Figure 1. Flowchart of preparation of the glycolic extract of *Aloe vera.* Source: Own authorship.

Table 1. Composition of *Aloe vera* gel.

Components	Quantities
Carbopol 940	1 g
Glycerin	5 g
EDTA	0.10 g
Propylene glycol	2.70 g
Methylparaben	0.20 g
Triethanolamine	1.15 g
Glycolic extract	10 mL
Water	q.s.p 100 g

Source: Adapted from *Formulário Nacional da Farmacopéia Brasileira* [11].

Determination of apparent density

The apparent density was determined in triplicate using 10 g of gel in heavy empty and filled beakers on an analytical balance and calculated from the formula [13]:

$$d = \frac{m}{v}$$

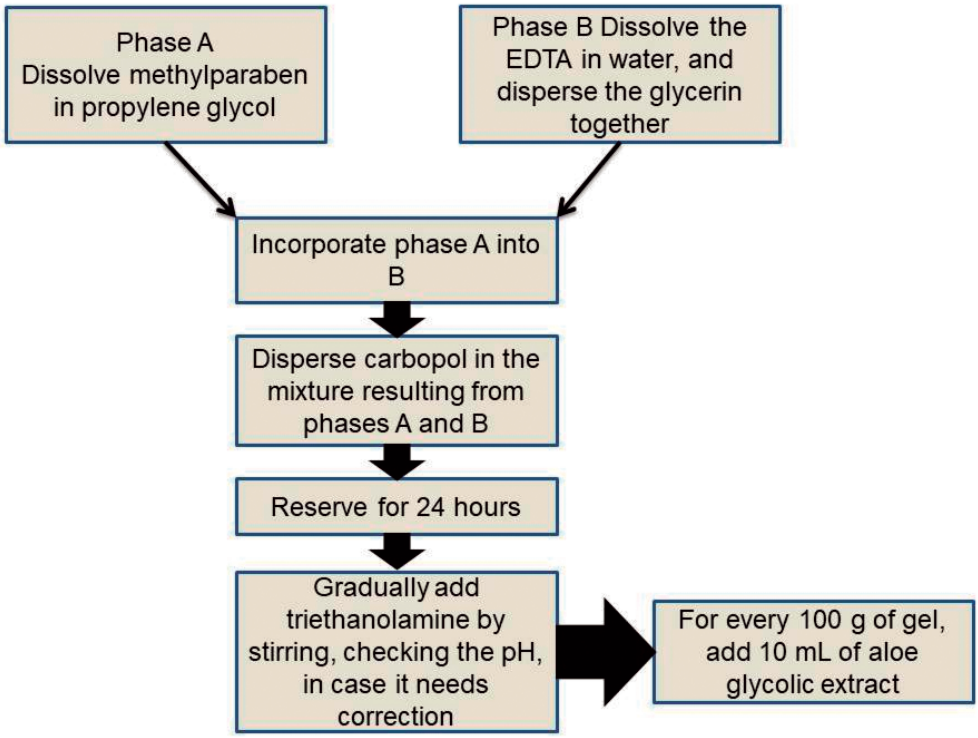

Figure 2. Flow chart of *Aloe vera* gel development. Source: Own authorship.

Determination of viscosity

The viscosity of the gel was evaluated by measuring the resistance to the rotation movement of metal axes when immersed in the liquid in a Brookfield rheometer [12]. Rotors 2, 3 and 4 were used, with a speed of 6 rpm and the calculation was performed using the following equation:

$$\eta = \kappa.\alpha$$

where, η is the absolute viscosity, κ is the coefficient, α is the reading indicated by the pointer.

Determination of spreadability

To determine the spreadability, the technique proposed by Knorst [14] was used, which uses glass plates on a scale of graph paper to determine the surface that the sample covers by measuring perpendicular diameters, with subsequent calculation of the area obtained in mm^2. 1 g of the sample was deposited in the central space of the plate

(20 x 20 cm), after which a glass plate of known mass was placed on the sample. After three minutes, the diameters covered by the sample were read in a horizontal position, using the graph paper and then the spreadability was calculated. This procedure was repeated by successively adding 250 g, 500 g, and 750 g weights in intervals of three minutes from one weight to another, the procedure was performed in triplicate. The spreadability of the samples was determined according to the added weight, according to the equation below [15].

$$Ei = d^2 \times \pi/4$$

where, *Ei:* Sample spreadability for a given weight in square millimeter (mm^2), *d*: Average diameter in millimeter (mm).

The spreadability factor (FE) was also calculated by:

$$FE = Ei/P$$

where, *Ei* = maximum spreading area (mm^2) and P = total added weight (g).

Centrifugation test

The centrifugation test produces stress in the sample, anticipating possible instabilities of the product, through a simulation in the increase in the force of gravity, and increasing the mobility of the particles [13]. 5 g of gel was weighed and placed in the centrifuge at three different rotations, respectively, 1000 rpm, 2500 rpm, 3000 rpm. For 15 minutes [16].

Organoleptic characteristics

The obtained gel was observed visually, in terms of appearance, color and odor [13].

Results and discussion

Organoleptic characteristics

Considering the suitability for the treatment of wounds by topical application, the gel obtained was evaluated for its physical-chemical properties. Such a semi-solid formulation is characterized as an aqueous vehicle with pleasant sensory and easy application on the skin. The gel containing glycolic extract of *Aloe vera* obtained, was homogeneous, translucent, shiny, odorless and without lumps as observed in figure 3.

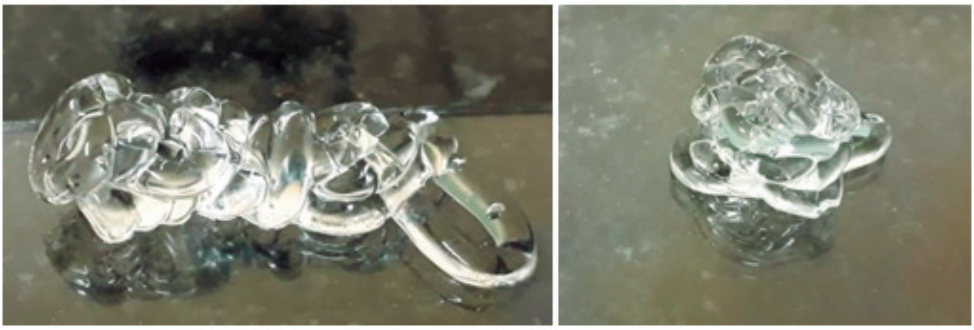

Figure 3. Visual aspect of the obtained gel. Source: Research archives, 2019.

The gel formulation is the choice, among topical semi-solid manipulation options, because in addition to ease of administration, it has high viscosity, good permanence, moisturizing effect on scaly skin, greater bio-adhesion and less potential for irritation [17].

Physical-chemical characteristics

The physical-chemical characteristics of the gel obtained are shown in table 2.

Table 2. Physicochemical characteristics of *Aloe vera* Gel (n = 3).

Test				
pH	**Apparent density (g/mL)**	**Viscosity (Cp)**	**Centrifugation**	**FE Spreadability (mm^2/g)**
5.44 ± 0.00	0.1018 ± 0.0008	> 10 000	No change	8.40 ± 3.6

Source: Research data, 2019.

pH

The pH value (5.44) was similar to that found by Borella *et al.* [18], in which he highlights small pH variations using Carbopol 940 in papain gels. The gel showed values according to the cutaneous pH which is slightly acid varying from 4.6 to 5.8, this acidity is a way of protecting the skin against microorganisms [19, 20]. The pH is an important parameter with regard to acute wounds since they have an alkaline pH, which predisposes to less healing, while acidic conditions help in this process [21, 22].

Apparent density

The apparent density of the aloe gel was 0.1018 ± 0.0008 (g/mL) and represents the relationship between the mass and the volume occupied by the sample. In liquids or

semi-solids this parameter may indicate the incorporation of air or the loss of volatile ingredients in the sample [13]. According to Pedrazzi *et al.* [23] the measure of the product density is dependent on the characteristics of the components present in its formulation, and also on the existence or not of incorporated air during the mixing process.

Viscosity

It was not possible to obtain an accurate viscosity value because it exceeded the maximum reading limit of the equipment used. Following the proposed formula and considering the maximum possible reading value (100), it can be said that the sample has viscosity above 10 000 cP. In addition, it is important to highlight that this finding is expected, since, according to Handbook of Pharmaceutical Excipients, carbomers such as Carbopol 940 have viscosity that can vary between 40 000 to 60 000 cP [24, 25].

The present study corroborates the research by De Aguiar [24] who tested gels based on Carbopol at different temperatures, including body temperature, in which it had a high viscosity, reinforcing that this group of gels has high consistency and good adherence. The evaluation of this component helps to define whether a product indicates the appropriate consistency or fluidity and can show whether the stability is adequate [13]. Thixotropy is a rheological characteristic referring to changes in viscosity with time of application [26].

Topically applied formulations should preferably be viscous when inert and become more fluid when administered to the skin [27]. The rheological characteristic referring to the change in viscosity with the application time is thixotropy [26], and according to Mateus *et al.* [22], an increase in the viscosity of the gel prolongs the release of the drug causing it to improve patient compliance with treatment as it will reduce the number of applications.

The type of polymer and its concentration influence the thixotropic characteristic of the gel. Base formulation with Carbopol presents a higher thixotropy, which is desirable together with its high viscosity, due to deformation in the application and soon after resuming its initial viscosity [28].

Spreadability

The expansion capacity of the semi-solid formulation against a given force (weight) for a time is defined as spreadability. Its determination is essential, as it is related to the ease of topical application of the product [29]. Spreadability is based on resistance to forced movement. The results correspond to the relationship between the spreading area, which will be caused by a force applied on the gel [30].

The graphical representation of the spreadability as a function of the applied mass (figure 4) revealed rheological behavior ranging from 1994.65 mm^2, when subjected to the weight of the glass plate, to 4042.97 mm^2 with the additional mass of 750 g.

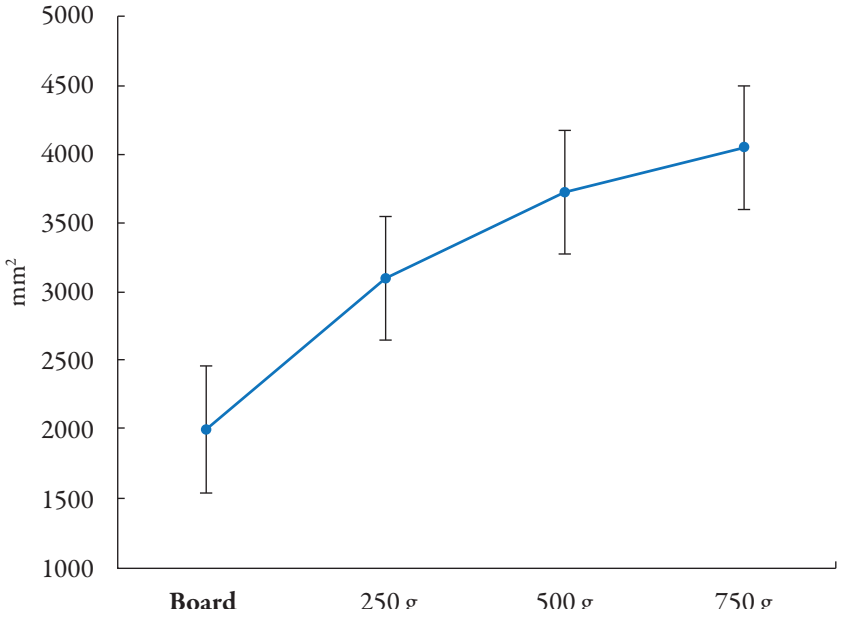

Figure 4. Representative graph of *Aloe vera* gel spreadability (n = 3). Source: Research Archives, 2019.

The spreadability factor of the aloe gel obtained with 1% carbopol was 8.40 ± 3.6 mm^2/g. Carbopol Ultrez hydrogels obtained by Paines *et al.* [31] containing clotrimazole and tea tree oil showed spreadability factors around 4.6 mm^2/g, but it is not clear the percentage of the polymer in the formulation.

Cordeiro *et al.* [30], in a technological development study and evaluation of the stability of dermatological gel based on ginger essential oil, showed that gel based on Carbopol 940 maintains its spreadability without the product draining during administration, even in the face of changes of temperatures, since it was exposed to a preliminary and accelerated stability study showing good physical stability of the formulation which contains Carbopol.

The uniform application of the gel on the skin depends on the spreadability, a good gel will spread easily, the spreadability will help the patient's adherence to the treatment as well as an easier application [32]. A good criterion for the gel to meet the qualities recommended by Organs regulatory bodies is the propagation capacity, which would be the extension of the area where the gel spreads easily at the time of use [33].

Centrifugation test

The centrifugation test represents a preliminary stability test, since, with increased gravity, it is demonstrated in advance if the product will show any type of instability [34]. After centrifugation in all conditions established for the test, the sample remained stable and without change in coalescence, phase changes, color, or odor, showing itself stable as seen in figure 5.

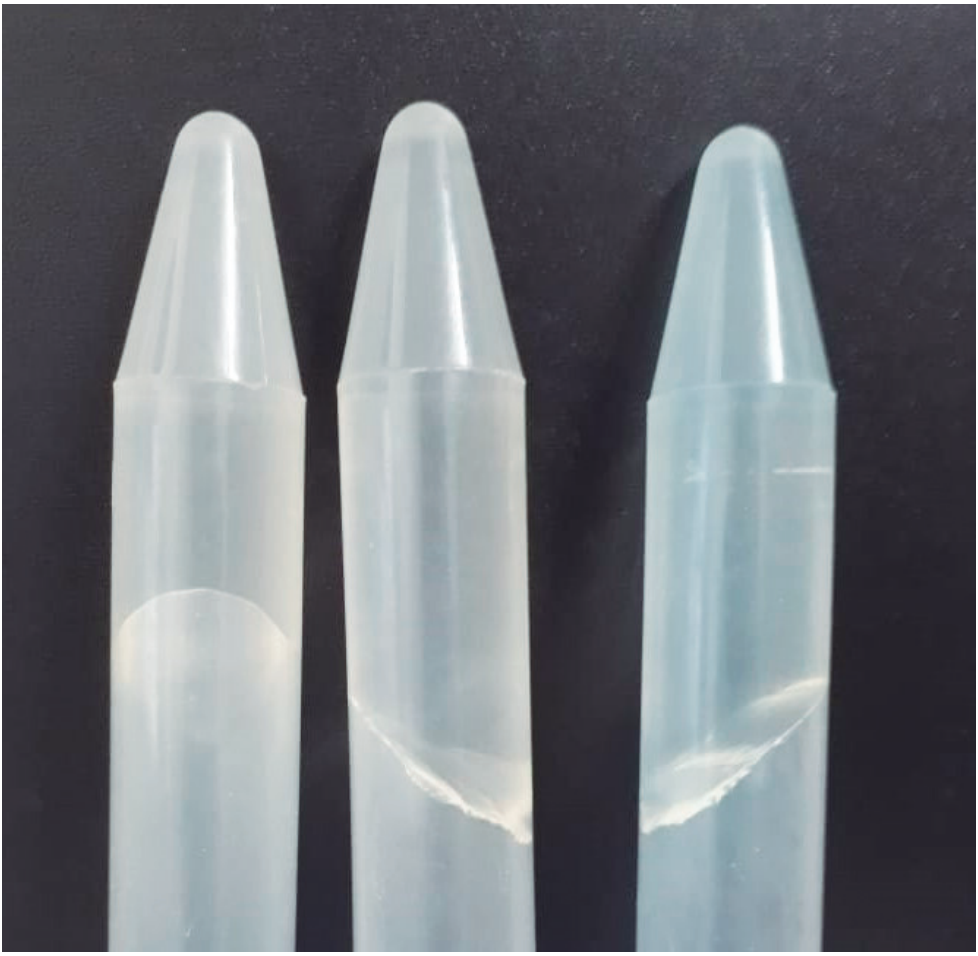

Figure 5. Visual aspect of the gel after the centrifugation test. Source: Research Archives, 2019.

Cordeiro *et al.* [30], and Coelho *et al.* [34] obtained similar results in preliminary stability in dermatological gel from ginger essential oil and gel containing guava leaf extract, respectively. The stability research contributes to: Guide the development of

the formulation and packaging material, serve as alternatives for improving the formulations, help to also determine the expiration date and control of organoleptic, physical-chemical and microbiological stability, producing information on the quality of the product. On the other hand, rheology represents the study of the flow and deformation properties of matter under the action of forces, whose behavior helps in the early detection of signs of instability in formulations, assuming paramount importance for the evaluation of semi-solid formulations [35, 36].

Conclusions

The gel formulated from glycolic extract of *Aloe vera* showed satisfactory organoleptic characteristics, with a homogeneous and shiny appearance, with no apparent odor and translucent color, without altering these characteristics; slightly acid pH, compatible with the skin, which favors wound healing; adequate rheological aspects with good viscosity and spreadability; no changes related to stability, under the conditions evaluated. The development of gels must be carried out consistently and taking into account the therapeutic potential of the present formulation for the treatment of wounds, it is suggested complementary studies regarding the microbiological quality, guaranteeing the safety of a product that presented a pleasant appearance and rheological characteristics, and promising stability.

Disclosure statement

No potential conflict of interest was reported by the authors.

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How to cite this article

I.H. Mendes-Aciole, F.P. de Andrade-Júnior, L. Vilar-Cordeiro, J.B. Pereira de Souza, Aloe gel: manipulation and characterization of physical-chemical quality adjustment, *Rev. Colomb. Cienc. Quím. Farm.*, **49**(3), 790-805 (2020).

Scientific research article / *http://dx.doi.org/10.15446/rcciquifa.v49n3.91346*

In silico approach of antiviral compounds potentials for SARS-CoV-2 and SARS-CoV and drug-like property predictions

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Received: 4 October 2019

Revised: 29 August 2020

Accepted: 31 August 2020

Summary

Introduction: SARS-CoV-2 (Coronavirus 2 of the severe acute respiratory syndrome; previously 2019-nCoV) and SARS-CoV (coronavirus of the severe acute respiratory syndrome) are closely related viruses, which have no treatment so far. Therefore, the search for new molecules is essential. *Objectives*: the objective of this study is to use *in silico* approach to propose antiviral compounds potential for SARS-CoV-2 and SARS-CoV and drug-like properties predictions. *Materials and methods*: Molecular docking were performed using AutoDock Vina with the molecules that had previously demonstrated drug-like properties. Subsequently, amino acids and the type of interaction involved in the protein-ligand complex were identified. *Results*: It was possible to identify six potential candidates available in the PubChem database capable of interacting with the 6U7 and 2GTB proteases, which bind to the same active site that lopinavir and remdesivir. *Conclusion*: Small molecules with drug-like properties could be used as antivirals, after experimental evaluations.

Key words: Coronavirus, small molecules, molecular docking, pandemic, antiviral treatments.

Resumen

Enfoque *in silico* de potenciales compuestos antivirales para SARS-CoV-2 Y SARS-CoV y predicción de propiedades *drug-like*

Introducción: los coronavirus SARS-CoV-2 (coronavirus del síndrome respiratorio agudo grave de tipo 2; previamente identificado como 2019-nCoV) y SARS-CoV (coronavirus del síndrome respiratorio agudo grave) son virus estrechamente relacionados, que no tienen tratamiento hasta el momento. Por lo tanto, la búsqueda de nuevas moléculas es esencial. *Objetivos*: el objetivo de este estudio es utilizar un enfoque *in silico* para proponer potenciales compuestos antivirales para el SARS-CoV-2 y el SARS-CoV y predicciones de propiedades "drug-like". *Materiales y métodos*: el acoplamiento molecular se realizó utilizando "AutoDock Vina" con las moléculas que previamente habían demostrado propiedades similares a los fármacos. Posteriormente, se identificaron los aminoácidos y el tipo de interacción involucrada en el complejo proteína-ligando. *Resultados*: fue posible identificar seis candidatos potenciales disponibles en la base de datos PubChem capaces de interactuar con las proteasas 6U7 y 2GTB, que se unen al mismo sitio activo al que se unen lopinavir y remdesivir. *Conclusiones*: moléculas pequeñas con propiedades similares a los fármacos podrían usarse como antivirales, después de evaluaciones experimentales.

Palabras clave: Coronavirus, pequeñas moléculas, acoplamiento molecular, pandemia, tratamientos antivirales.

Introduction

Coronaviruses are enveloped positive single-stranded large RNA viruses that infect humans, but also a wide range of animals [1]. According to their morphology as spherical virions with a central nucleus and surface projections that resemble a solar corona, they were called coronaviruses [2]. There are four subfamilies, namely alpha, beta, gamma, and delta coronavirus [1]. The size of the genome varies between 26 kb and 32 kb [3]. Among the coronavirus subtypes that can infect humans, beta-coronaviruses can cause serious illness and death, while alpha-coronaviruses cause asymptomatic or mildly symptomatic infections [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the B-lineage of beta-coronaviruses and is closely related to the SARS-CoV virus [1]. There are four major structural proteins encoded by the coronaviral genome in the envelope, one of which is the spike protein (S) that binds to the angiotensin-converting enzyme 2 (ACE2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell [2].

The world is currently facing a SARS-CoV-2 pandemic, declared by the World Health Organization (WHO) Emergency Committee on March 11, 2020, based on rising case notification rates in different countries. This virus has spread to 188 countries as of August 10 and has infected more than 19.995.057 people. The case detection rate changes daily and can be tracked in near real-time on the website provided by Johns Hopkins University and other forums [4]. Most worrying is that the disease has posed a serious threat to global public health, by requiring the development of safe and effective prophylactic and therapeutic drugs against the infection of its causative agent, SARS-CoV-2, also known as the new coronavirus 2019 (2019-nCoV) [3]. Therefore, the lack of specific medications to prevent and treat an attack is an important need at the present time, considering that the available treatment is clearly symptomatic [5]. Drug discovery can also be accelerated by applying new detection techniques, including computational approaches, to identify antivirals that could be ready for large-scale clinical trials in a matter of weeks [6].

The main pharmacological targets for coronavirus (CoV) are spike protein, envelope protein, membrane protein, protease, nucleocapsid protein, hemagglutinin esterase, and helicase, for which drug design can be considered. There are 16 other non-structural proteins (NSP) that can also be considered from the perspective of drug design including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro). These proteins are important because upon entering host cells, the viral genome is released as a single-stranded positive RNA. Subsequently, it is translated into viral polyproteins using host cell protein translation machinery, which is then cleaved into effector proteins by viral proteins 3CLpro and PLpro. PLpro also behaves like a deubiquitinase that can de-position certain proteins from the host cell, including interferon factor 3 and NF-κB, resulting in immune suppression. RdRp synthesizes a full-length negative-strand RNA template to be used by RdRp to produce more viral genomic RNA [7]. 3CLpro is a key CoV enzyme, which plays a key role in mediating viral replication and transcription, making it an attractive drug target for this virus [7-8]. This protein was selected to be used as a pharmacological target in this study. Lopinavir is an antiretroviral drug used in patients with HIV and Remdesivir is an antiviral prodrug used to treat Ebola virus disease, currently these two drugs have been proposed as antivirals for SAR-CoV-2. Lopinavir and remdesivir are antiviral agents [7].

Therefore, the main structural proteins and NSP can play an important role in the perspective of drug design. However, the occurrence of frequent recombination events is an important deterrent towards the development of vaccines and medications specific to CoV [9]. The objective of this study is to use *in silico* approach to propose antiviral compounds potential for SARS-CoV-2 and SARS-CoV and drug-like properties predictions.

Methods

Equipment and Software

Drug Likeness Tool (DruLiTo 1) was used to detect molecules with ADME properties. AutoDock Vina was the primary docking programs used in this work [10]. The preparation of the PDBQT files and determination of the grid box size was carried out using Auto-Dock Tools version 1.1. Chimera was utilized to prepare protein structures. PyMol (DeLano Scientific LLC, USA) was employed to visualize protein-ligand complex structures. The identification of protein residues that interact with small molecules was carried out employing LigandScout. Computational studies were carried out using a machine running on Inter Core i7 4.0GHZ, a processor with 8GB RAM and 1TB hard disk.

Selection of molecules with properties drug-likeness

The database PubChem was used to download 3 million molecules deposited during 2015 and 2016. These chemicals were filtered considering those having characteristics of drugs-like, to filter molecules were used free software Drug Likeness Tool (DruLiTo 1). The rules Lipinski that predict if a compound is more likely to be membrane-permeable and easily absorbed by the body [11]. Veber rule, to predict good oral bioavailability [12]. Ghose filter that defines drug-likeness constraints [13]. The molecules that passed these filters were selected for molecular docking. The criteria that were taken into account were: molecular weight ≤ 500, Log *P* ≤ 5, H-Bond donor ≤ 5, H-bond acceptor ≤ 10, rotatable bond ≤ 10, polar surface area ≤ 140, Atom-Count from 20 to 70 and refractivity from 40 to 130. Of the three million molecules discharged in PubChem, only 997 passed the drug-like filters, that is, they possess drug-like properties.

Protein structure preparation

The 3D structure of proteins: COVID-19 main protease and SARS coronavirus main peptidase were downloaded from Protein Data Bank (PDB: 6LU7 and 2GTB, respectively), both obtained by x-ray diffraction, and prepared with Chimera. The water molecules and other ligands present in the proteins were eliminated. Proteins were minimized using atomic partial charges by Kollman method, which describes the potential of the system in terms of the energy positions of the atoms and is parameterized for proteins and nucleic acids [14]. MGLTools 1.5.0 software was utilized to convert structures from PDB to PDBQT format, adding polar hydrogens and assigning Kollman partial charges [14].

Protein-ligand docking

Molecular docking was performed using AutoDock Vina is a virtual molecular docking and screening program. Vina uses a sophisticated gradient optimization method in his local optimization procedure. The gradient calculation effectively provides the optimization algorithm with a "sense of direction" from a single evaluation. By using multithreading, Vina can further speed up execution by leveraging multiple CPUs or CPU cores. The docking site for ligands on evaluated proteins was defined by establishing a cube with a sufficient dimension to cover the complete protein, with a grid point spacing of 1 Å for the proteins. Three runs were carried out by ligand, and for each run the best pose was saved. Finally, the average binding affinity for best poses was accepted as the binding affinity value for a particular complex [14]. The three-best protein-ligand complexes were selected, those that showed the highest affinity value.

Identifying interactions

Three ligand structures were selected and coupled with proteins to identify residues of proteins that interact with small molecules, using Ligand scout software. This program proposes the number and type of primary existing ligand–residue interactions on the protein active site. For this, the coordinates generated during molecular coupling are used, to identify the amino acids participating in the protein-ligand interaction.

Results

In this study of the 3 million new molecules selected, only 997 met drug-like properties (rules Lipinski, Veber rule, and Ghose filter), which were used to make molecular docking. These molecules possess ADME properties and also have a high affinity for all proteins (molecules with scores below -7.8 kcal/mol) (table 1 and figure 1), this value represents the affinity of a protein for a ligand as a semi-quantitative parameter related to the inverse of the dissociation constant. Therefore, only the three molecules for each protein with higher affinity values were selected as possible candidates.

The three-best protein-ligand complexes were selected and are shown in figures 2 and 3 for each protein, SARS coronavirus main peptidase (2GTB), and COVID-19 main protease (6LU7). 6LU7 is the main protease (M^{pro}) found in SARS-CoV-2 and 2GTB is the main protease found in the SARS-CoV [15]. With both proteins, blind molecular docking was carried out, that is, docking over the entire surface of the protein. Furthermore, molecular docking was performed using the same protocol with two antiviral drugs, in order to validate the binding site of the ligands evaluated by comparison with lopinavir and remdesivir.

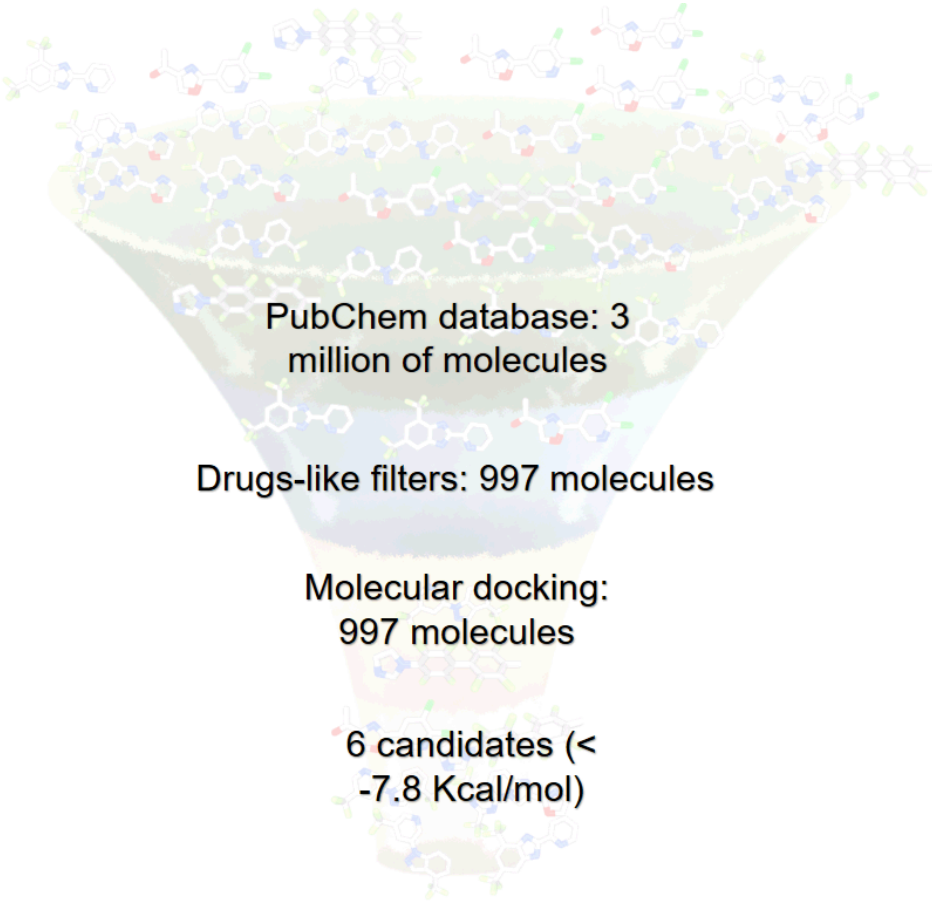

Figure 1. Flowchart for selecting the best protein-ligand complexes. Source: Own elaboration.

Table 2 shows the amino acids found in the active site pockets of 6LU7 and 2GTB in the complex with two reported inhibitors (lopinavir and remdesivir) and the selected new molecules selected.

The affinity values and three-dimensional view of the complexes with lopinavir and remdesivir are shown in figure 4. Lopinavir and remdesivir are two antiviral drugs against a clinical isolate of SARS-CoV-2 *in vitro* (7). In this study, we have used them to check the ability of the proposed new molecules to bind to the same active site of the proteins evaluated to which these two antiviral agents used in the treatment of SARS-CoV-2 and SARS-CoV bind. Being able to identify that the amino acid residues that participate in the formation of the protein-ligand complex were also identified in the protein-ligand complexes of the molecules with the best affinity values (table 1 and 2). The predominant type of interaction was the hydrophobic type interaction.

Table 1. Drug-like properties and AutoDock-calculated affinities obtained for docking of best molecules on proteins of COVID-19 (< -7.8 kcal/mol).

Compounds	Drug-like properties					Protein affinity (kcal/mol)
	MW (g/mol)	Log *P*	LRV	GFV	VRV	2GTB
CID 90252773 (4-(Trifluoromethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]indazole)	331.22	2.578	0*	0	0	-8,2
CID 90381721 (2-[10,12-Bis(trifluoromethyl)-2,5,11,13-tetrazatricyclo[7.4.0.02,6] trideca-1(13),3,5,7,9,11-hexaen-4-yl]-1,3-oxazole)	373.21	1.963	0	0	0	-8,6
CID 90380837 (1-[2-(5,6-Dichloropyridin-3-yl) -1,3-oxazol-4-yl]ethanone)	257.07	1.384	0	0	0	-8.5
Lopinavir	628.35	3.688	1	1	1	-8.4
Remdesivir	602.23	0.336	1	1	1	
						6LU7
CID 90178936 (1-[2,3,5,6-Tetrafluoro-4-(2,3,5,6-tetrafluoro-4-methylphenyl) phenyl]imidazole)	378.22	2.63	0	0	0	-8,0
CID 90364642 (2-Pyridin-2-yl-4,6-bis(trifluoromethyl) -1H-benzimidazole)	331.22	2.735	0	0	0	-8,1
CID 90380837 (1-[2-(5,6-Dichloropyridin-3-yl) -1,3-oxazol-4-yl]ethanone)	257.07	1.384	0	0	0	-7.8
Lopinavir	628.35	3.688	1	1	1	-8.3
Remdesivir	602.23	0.336	1	1	1	

MW: Molecular weight

Log *P*: Logarithm of octanol/water partition coefficient

LRV: Lipinski rule of 5 violations: Maximum is 4 violations

GF: Ghose Filter violation

VR: Vebers Rule violation

*This value refers to the number of violations found for each drug-like filter evaluated.

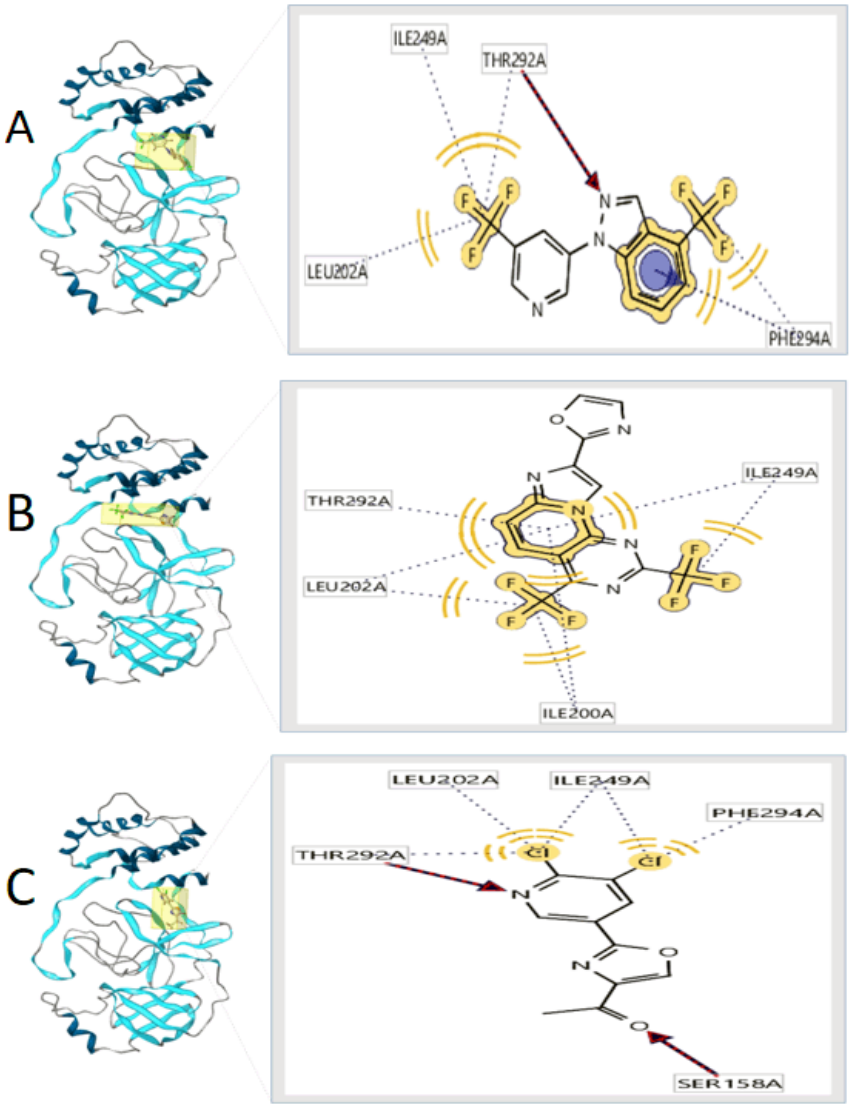

Figure 2. 3D view and interacting residues present in proteins 2GTB. A: 2GTB -90252773, B: 2GTB -90381721, C: 2GTB -90380837. Source: Own elaboration.

Discussion

SARS-CoV-2 represents a pandemic threat to public health because there is no treatment to counteract the virus [16]. So the search for new molecules with antiviral properties is imperative [7]. The present study focused on the main proteases

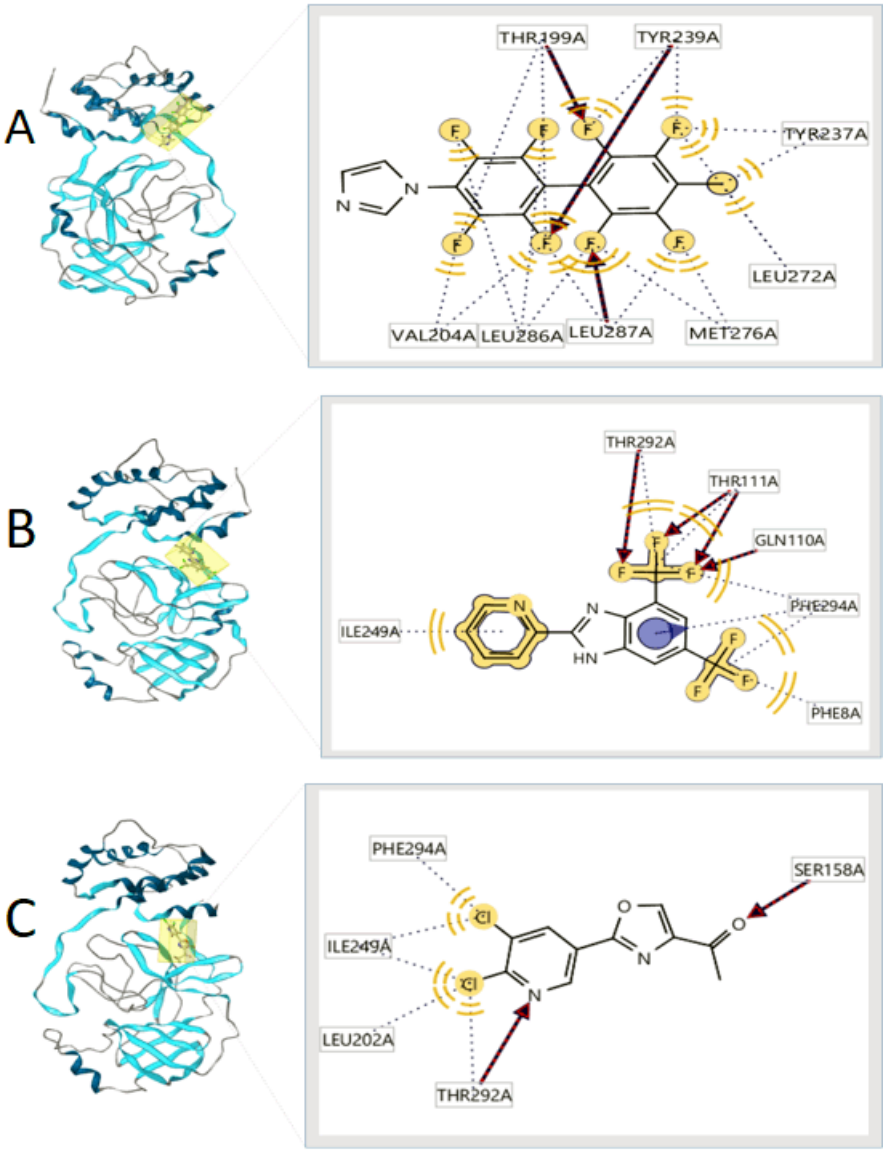

Figure 3. 3D view and interacting residues present in proteins 6LU7. A: 6LU7 -90178936, B: 6LU7 -90364642, C: 6LU7 -90380837. Source: Own elaboration.

in CoVs (3CLpro/M^{pro}), especially PDB ID 6LU7, as potential target proteins for SARS-CoV-2 treatment [15] and is the main peptidase of the SARS coronavirus (SARS-CoV M (pro)), which plays an essential role in the life cycle of the virus and is a main target for the development of anti-SARS agents [17]. Xu *et al.* [18] mentioned

Table 2. Interacting residues 2GTB and 6LU7 protein - inhibitor complex in comparison with ligands studied.

Interaction 2GTB in complex with inhibitor					
Name	**Amino acid**	**Type of interaction**	**Interaction identified in the protein - ligand complexes**		
			90252773	**90381721**	**90380837**
Lopinavir	Phe294	Aromatic ring	X	-*	X
	Thr292	Hydrophobic	X	X	X
	Leu202	Hydrophobic	X	X	X
	Ile249	Hydrophobic	X	X	X
	Val297	Hydrophobic	-	-	-
	Ile106	Hydrophobic	-	-	-
	Val104	Hydrophobic			
Remdesivir	Phe294	Hydrophobic	X	-	X
	Val297	Hydrophobic	-	-	-
	Leu253	Hydrophobic	-	-	-
	Ile249	Hydrophobic	X	X	X
	Thr292	Hydrophobic	X	X	X
	Leu202	Hydrophobic	X	X	X
	Gln110	H bond acceptor	-	-	-
	Asn151	H bond donor	-	-	-
	Thr111	H bond donor	-	-	-
	Ile106	Hydrophobic	-	-	-
Interaction 6LU7 in complex with inhibitor					
			90178936	**90364642**	**90380837**
Lopinavir	Val202	Hydrophobic	-	-	-
	Ile249	Hydrophobic	-	X	X
	Phe294	Aromatic ring	-	X	X
	Val104	Hydrophobic	-	-	-
	Ile106	Hydrophobic	-	-	-

(*Continued*)

Table 2. Interacting residues 2GTB and 6LU7 protein - inhibitor complex in comparison with ligands studied.

Interaction 6LU7 in complex with inhibitor					
Remdesivir	Thr199	H bond acceptor	X	-	-
	Tyr239	H bond acceptor	X	-	-
	Leu286	Hydrophobic	X	-	-
	Leu271	Hydrophobic	-	-	-
	Met276	Hydrophobic	X	-	-
	Leu272	Hydrophobic	-	-	-
	Tyr237	Hydrophobic	X	-	-
	Leu287	H bond acceptor	X	-	-
	Asp289	H bond donor	-	-	-

*The presence of the amino acid in the protein-ligand complex of the proposed candidates was not identified.

that the main protease in 2019-nCoV shares 96% similarity with that in SARS0 [14]. To make comparisons, these two proteins were used.

In the search for new molecules that can be used as antivirals, it is important to predict the similarity of the drugs, as well as the intestinal absorption capacity and bioavailability requirements [19]. In this study, the selected chemical compounds meet these. As for the affinities obtained, they are comparable with those obtained for lopinavir and remdesivir. Khaerunnisa *et al.*, [15] reported that the binding energies obtained from the docking of 6LU7 with native ligand, nelfinavir, lopinavir, kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate, zingerol, gingerol, and allicin were -8.37, -10.72, -9.41, -8.58, -8.47, -8.17, -7.99, -7.89, -7.83, -7.31, -7.05, -7.24, -6.67, -5.40, -5.38, and -4.03 kcal/mol, respectively. As can be seen, the affinity values reported using AutoDock and the same protein are comparable with those obtained in this study.

Several authors [15, 20, 21] have reported new molecules with antiviral properties against SARS-CoV-2 through molecular docking with affinity values comparable to those obtained in this study. For the main peptidase of the SARS coronavirus, the protein-ligand complex (2GTB -90252773, B. 2GTB -90381721, C. 2GTB -90380837) show that all bind to the same active site including lopinavir and remdesivir, involving the same amino acids and the same type of interactions, being the interactions of hydrophobic type the main ones found. The protein complexes binding to the 6LU7

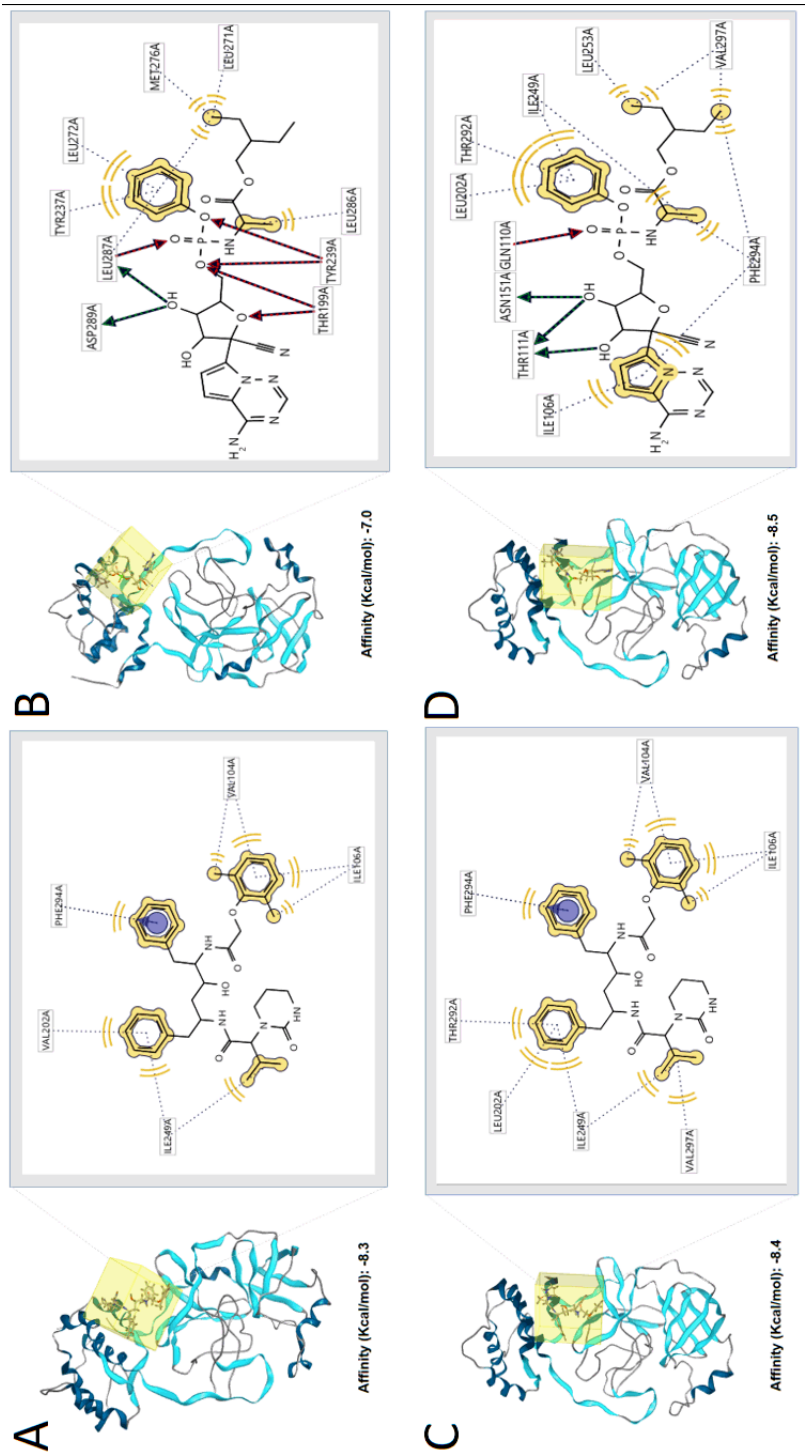

Figure 4. 3D view and interacting residues present 2GTB and 6LU7 protein - inhibitor complex. A: 6LU7 -Lopinavir, B: 6LU7 -Remdesivir, C: 2GTB – Lopinavir, D: 2GTB – Remdesivir. Source: Own elaboration.

protein show that the 6LU7-90364642 and 6LU7-90380837 complexes bind to the same site as lopinavir, but the 6LU7-90178936 complex interacts at a different site together with remdenavir, which leads us to think of a possible allosteric site of interaction, in which other amino acids with predominantly hydrophobic interactions are involved. Chauhan [21], reported that remdesivir couples with 6LU7 with an affinity value of -13.1. Khalifa *et al.* [22], reported that tellimagradin interacts within the protease binding pocket with the amino acids Phe294, Thr292, Ile249, among others, which were also identified in our protein-ligand complexes. These results suggest that small molecules identified by *in silico* approaches and with drug-like properties may be useful candidates for the development of new antiviral drugs. These molecules are available in the PubChem database and can be used to carry out experimental studies.

The results obtained are of great importance because they allow us to identify potential molecules with antiviral characteristics using an *in silico* approach, which reduces the time and budget required in the laborious search for a treatment to stop the progression of this disease that is affecting millions of people in the world. In this study, it is recommended to continue to a next phase in drug development, which consists of conducting in vitro and in vivo evaluation with the proposed candidates, to develop new drugs against SARS-CoV-2 and SARS-CoV.

Conclusions

The protein-ligand complexes 2GTB -90252773, 2GTB -90381721, 2GTB -90380837, 6LU7-90364642, 6LU7-90380837 and 6LU7-90178936 were those that showed the highest affinity values (< -7.8), with the ability to interact in the same binding sites for lopinavir and remdenavir, being potential candidates with drug-like properties to act as antivirals against SARS-COV and SARS-CoV-2. These molecules can be evaluated by pharmacological experimentation.

Acknowledgements

The authors want to thank the University of Sucre.

Disclosure statement

No potential conflict of interest was reported by the authors.

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How to cite this article

N. Pajaro-Castro, C. Ibañez-Bersinger, G. Leon-Mendez, *In silico* approach of antiviral compounds potentials for SARS-CoV-2 and SARS-CoV and drug-like property predictions, *Rev. Colomb. Cienc. Quím. Farm.*, **49**(3), 806-821 (2020).

Scientific research article / *http://dx.doi.org/10.15446/rcciquifa.v49n3.91347*

Prediction of sulfadiazine solubility in some cosolvent mixtures using non-ideal solution models

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Received: 19 September 2020

Revised: 28 September 2020

Accepted: 30 September 2020

Summary

The experimental data of sulfadiazine in (methanol + water), (ethanol + water) and (1-propanol + water) cosolvent mixtures at some temperatures were correlated using non-ideal solution models, namely, the modified Apelblat and Buchowski-Ksiazaczak equations and the van't Hoff equation. The calculated results agreed well with the experimental data. According to the Buchowski equation, the solubility of sulfadiazine in the three co-solvent mixtures shows important deviations from ideality, which is consistent with the literature.

Key words: Sulfadiazine, solubility, van't Hoff model, Buchowski-Ksiazaczak λh model, Apelblat model.

Resumen

Predicción de la solubilidad de la sulfadiazina en algunas mezclas cosolventes utilizando modelos de solución no ideales

Los datos experimentales de sulfadiazina en mezclas de cosolvente de (metanol + agua), (etanol + agua) y (1-propanol + agua) a algunas temperaturas se correlacionaron utilizando modelos de solución no ideales, a saber, las ecuaciones modificadas de Apelblat y Buchowski y la ecuación de van't Hoff. Los resultados calculados coincidieron bien con los datos experimentales. Según la ecuación de Buchowski, la solubilidad de la sulfadiazina en las tres mezclas de cosolventes muestra importantes desviaciones de la idealidad, lo que concuerda con la literatura.

Palabras clave: Sulfadiazina, solubilidad, modelo de van't Hoff, modelo de Buchowski-Ksiazaczak λh, modelo de Apelblat.

Introduction

Sulfadiazine (N^1-2-pyrimidinylsulfanilamide) (figure 1) is a member of the sulfonamide family [1]. As one of the earliest antibacterial drugs used in the prevention and treatment of bacterial infections, sulfonamides are widely used in the medical and livestock industries due to their broad antibacterial spectrum, stability and low-cost [2-4], however, sulfadiazine solubility in ambient water is very low and it is considered as practically insoluble [5-8]. Although the solid dosage form of sulfadiazine has been widely used in therapeutics, the development of liquid dosage forms is important to administer the drug to special groups of patients. To increase the solubility of sulfadiazine some cosolvents have been added to water [9, 10]. The analysis of sulfadiazine in the pharmaceutical industry typically involves high-performance liquid chromatograph that consumes a large quantity of hazardous organic solvents and its waste needs to be properly disposed of [11, 12].

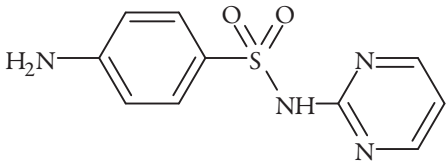

Figure 1. Molecular structure of sulfadiazine.

However, solubility measurement and optimization of the solvent composition for dissolving a desired amount of a drug in a given volume of the solution in most of the cases is a laborious and time consuming procedure which may cause some limitations in discovering and development of new drugs [13, 14]. Mathematical model, as an alternative method, could be used to estimate drug's solubility especially when the solid–liquid equilibrium measurements become impractical. Various numerical models proposed for the estimation of the solubility of drug and/or drug like compounds in the cosolvency systems which in order of appearance include van't Hoff equation [15], Yalkowsky model [5, 16, 17], the mixture response surface model, the double log-log model, the modified Wilson model[18], the Jouyban-Acree model [19-21], the Jouyban-Acree-van't Hoff model, and modified Jouyban-Acree-van't Hoff model. Van't Hoff equation predicts solubility at different temperatures in each solvent composition [22, 23], whereas Yalkowsky model, the modified Wilson model [18], the double log-log model and mixture response surface model predict solubility at different solvent mixtures. Whereas, the Jouyban-Acree [24] and Jouyban-Acree-van't Hoff models [25] predict the solubility in various solvent composition at different temperatures.

The objective of the present work is to evaluate the application of the van't Hoff, Buchowski-Ksiazaczak λh, and modified Apelblat models to the solubility of sulfadiazine in three cosolvent systems.

Theoretical

Modified Apelblat equation

From the Williamson equation, the solubility of non-electrolytes is expressed as [26]:

$$\frac{\partial \ln\left(m/m^{o}\right)}{\partial T^{-1}} = \frac{\Delta_{\text{soln}} H(T)}{R\left[1-0.001hM_1 m\right] f}, f = 1 + \left\{ \frac{\partial \ln \gamma_3}{\partial \ln\left(m/m^{o}\right)} \right\}_T, \tag{1}$$

where h denotes a number of water molecules in the hydrate, $\Delta_{\text{soln}}H(T)$ is the molar enthalpy of solution, γ_3 is the activity coefficient of the solute, M_1 is the molar mass of solvent, R is the gas constant and $m^{\circ} = 1$ mol.kg^{-1}.

If it is assumed that the enthalpy of solution depends linearly on the temperature, the integral form of equation (1) is [27]:

$$\ln\left(m/m^{\circ}\right) = A + BT^{-1} + C\ln T \tag{2}$$

So, expressing the solubility in mole fraction, the modified Apelblat equation, which is a semi-empirical model derived from solid-liquid equilibrium is [28]:

$$\ln x_3 = A + BT^{-1} + C\ln T \tag{3}$$

x_1 refers to measured mole fraction solubility of drug in selected solvent at absolute temperature T; A and B reflect the variation in the solution activity coefficient; C represents the influence of temperature on enthalpy of fusion [29, 30]; The above three parameters and experimental prediction values can be obtained by the nonlinear regression method in Python.

Van't Hoff equation

The van't Hoff equation is also a semi-empirical equation, which reveals the relationship between the mole fraction solubility and the temperature in an ideal solution by taking the solvent effect into account. The formula is shown as equation (4).

$$\ln x_3 = A + \frac{B}{T} \tag{4}$$

A and B are parameters, which can be related to thermodynamic parameters such as dissolution enthalpy and dissolution entropy [22]. The above can be shown from the two mathematical expressions for the Gibbs energy [31-34]:

$$\Delta_{soln} G^\circ = -RT \ln x_3 \tag{5}$$

$$\Delta_{soln} G^\circ = \Delta_{soln} H^\circ - T\Delta_{soln} S^\circ \tag{6}$$

Solving for $\Delta_{soln} G^\circ$ from equation (5), subsequently replacing $\Delta_{soln} G^\circ$ from equation (6), we obtain,

$$\ln x_3 = -\frac{\Delta_{soln} G^\circ}{RT} = \frac{\Delta_{soln} H^\circ - T\Delta_{soln} S^\circ}{RT} \tag{7}$$

$$\ln x_3 = -\frac{\Delta_{soln} H^\circ}{RT} + \frac{\Delta_{soln} S^\circ}{R} \tag{8}$$

So,

$$A = -\frac{\Delta_{soln} H^\circ}{RT}; B = \frac{\Delta_{soln} S^\circ}{R} \tag{9}$$

Buchowski-Ksiazaczak λh model

In 1980, based on the generalized relationship, the Buchowski-Ksiazaczak λh equation was first proposed, which contains two parameters and is widely used to correlate solubility data. The Buchowski-Ksiazaczak λh equation is shown in equation (10).

$$\ln\left[1 + \frac{\lambda(1 - x_3)}{x_3}\right] = \lambda h\left(\frac{1}{T} - \frac{1}{T_f}\right) \tag{10}$$

where λ and h are the two parameters of the λh model, and T_f represents the melting point of drug [35-37]. The model can be tested starting from the following identity [38]:

$$\frac{\partial \ln(1 - a_1)}{\partial \ln a_1} = \frac{-a_1}{1 - a_1} \tag{11}$$

Integrating the identity –equation (11)– into the equation of into the Gibbs-Duhem equation, we obtain,

$$\frac{-a_1}{1-a_1}\frac{x_3}{x_1}=\left(\frac{\partial \ln(1-a_1)}{\partial \ln a_3}\right)_T \equiv \lambda \tag{12}$$

In this way λ is related to activity and therefore to the concept of ideality.

Buchowski showed that when graphing $\ln(1-a)$ vs $1/T$, a linear function was obtained whose slope is λh

$$\frac{\partial \ln(1-a_3)}{\partial T^{-1}}=\lambda h \tag{13}$$

Integration of equation (13) from T_m to T gives equation (14).

$$-\ln(1-a_3)_{sat}=\lambda h\left(\frac{1}{T}-\frac{1}{T_m}\right) \tag{14}$$

where T_m is the melting temperature.

For the solubility curve, equation (14) is rearranged as:

$$\frac{\lambda(1-x_3)}{x_3}=\frac{a_1}{1-a_1} \tag{15}$$

Hence,

$$-\ln(1-a_1)=\ln\left[1+\lambda(1-x_3)/x_3\right] \tag{16}$$

So, equations (14) and (16) give the solubility curve:

$$\ln\left[1+\frac{\lambda(1-x_3)}{x_3}\right]_{sat}=\lambda h\left(\frac{1}{T}-\frac{1}{T_m}\right) \tag{17}$$

Equation (17) is equal to equation (10).

Results and discussion

The solubilities of sulfadiazine in mixtures of (methanol + water), (ethanol + water) and (1-propanol + water) were provided by Delgado and Martínez [6-8].

The experimental solubility data were correlated with the van't Hoff equation, Apelblat equation and Buchowski–Ksiazaczak λh equation, using the software with the Python version 3.8 using pandas and NumPy library, the parameters of the models were calculated with SciPy library and plots were made with Plotly library.

Table 1 shows the parameters of the equations of λh, van't Hoff and Apelblat, for the solubility of SD in (methanol + water) co-solvent mixtures. Although Delgado and Martínez implements the van't Hoff equation, the purpose is to calculate the thermodynamic functions as shown in other references [39-42], and not, to use the equation to calculate the solubility at different temperatures regarding the experimental ones [43, 44]. The melting temperature data, necessary for the development of the λh model, was taken from the literature (259.5 °C) [6].

Table 1. The λh, van't Hoff and Apelblat equations parameters for sulfadiazine in (methanol + water) cosolvent mixtures.

w_1	λh		van't Hoff		Apelblat		
	λ	h	a	b	A	B	C
0.0	0.012	453579.478	-5240.132	5.381	721.839	-37592.530	-106.700
0.1	0.024	231338.674	-5471.214	6.531	-450.653	15179.951	68.083
0.2	0.048	117837.137	-5637.581	7.547	-245.459	5818.116	37.662
0.3	0.102	55545.250	-5641.050	8.306	-873.483	34189.980	131.315
0.4	0.091	58195.968	-5271.480	7.499	127.882	-10687.332	-17.940
0.5	0.071	67026.233	-4794.893	6.372	-636.382	24238.424	95.718
0.6	0.065	68272.846	-4436.498	5.607	-453.188	16284.888	68.325
0.7	0.055	74423.661	-4130.908	4.883	-1134.337	47356.976	169.635
0.8	0.048	80928.039	-3886.460	4.284	-591.953	23047.998	88.790
0.9	0.042	87512.255	-3735.108	3.886	-461.868	17310.056	69.356
1.0	0.033	105595.312	-3502.490	3.205	44.861	-5385.482	-6.203

Table 2 shows the calculated solubility using each of the exposed models, and the relative deviation, calculated using equation (18) [45-48].

$$DR = 100\left(\left|x_3^{Exp} - x_3^{Cal}\right|\right)\left(x_3^{Exp}\right)^{-1} \quad (18)$$

Table 2. Calculated solubility of sulfadiazine in (methanol + water) mixtures expressed in mole fraction ($10^4 x_3$), from equations of λh, van't Hoff and Apelblat.

Buchowski–Ksiazaczak λh equation										
w_1	**293.15 K**	**RD**	**298.15 K**	**RD**	303.15 K	**RD**	**308.15 K**	**RD**	**313.15 K**	**RD**
0.0	0.375	1.326	0.506	5.195	0.676	4.788	0.895	1.771	1.174	2.988
0.1	0.538	1.459	0.736	0.185	0.996	2.230	1.335	1.045	1.772	1.603
0.2	0.843	0.841	1.163	1.791	1.589	0.202	2.149	2.153	2.878	0.960
0.3	1.780	6.404	2.457	4.582	3.357	4.038	4.540	0.833	6.082	2.702
0.4	2.801	1.866	3.786	2.549	5.068	0.200	6.720	0.015	8.831	0.557
0.5	4.613	2.671	6.068	0.347	7.911	3.472	10.226	1.072	13.111	2.139
0.6	7.291	2.672	9.396	0.525	12.008	4.118	15.227	0.660	19.165	1.223
0.7	10.019	3.404	12.686	1.356	15.940	4.728	19.883	4.183	24.632	3.907
0.8	12.674	2.996	15.824	1.819	19.617	1.607	24.153	1.704	29.547	2.066
0.9	14.267	0.861	17.659	1.638	21.708	2.939	26.513	1.268	32.183	1.657
1.0	15.960	1.356	19.493	1.955	23.657	0.316	28.538	1.515	34.229	0.633
van't Hoff equation										
0.0	0.375	1.328	0.506	5.199	0.676	4.784	0.895	1.769	1.174	2.980
0.1	0.538	1.464	0.736	0.185	0.996	2.234	1.335	1.049	1.772	1.605
0.2	0.843	0.838	1.163	1.790	1.589	0.199	2.149	2.155	2.878	0.962
0.3	1.779	6.410	2.457	4.582	3.357	4.041	4.540	0.836	6.082	2.701
0.4	2.800	1.862	3.786	2.546	5.068	0.204	6.720	0.013	8.831	0.551
0.5	4.613	2.684	6.068	0.347	7.912	3.479	10.227	1.079	13.111	2.140
0.6	7.290	2.689	9.396	0.526	12.010	4.129	15.228	0.650	19.164	1.226
0.7	10.015	3.438	12.685	1.360	15.942	4.742	19.887	4.201	24.633	3.902
0.8	12.670	3.028	15.825	1.820	19.620	1.625	24.157	1.721	29.546	2.070
0.9	14.262	0.893	17.659	1.635	21.713	2.960	26.518	1.285	32.180	1.665
1.0	15.955	1.384	19.495	1.965	23.663	0.341	28.542	1.501	34.221	0.610

(*Continued*)

Table 2. Calculated solubility of sulfadiazine in (methanol + water) mixtures expressed in mole fraction ($10^4 x_3$), from equations of λh, van't Hoff and Apelblat.

w_1	**293.15 K**	**RD**	**298.15 K**	**RD**	303.15 K	**RD**	**308.15 K**	**RD**	**313.15 K**	**RD**
Apelblat equation										
0.0	0.363	4.561	0.513	6.566	0.695	2.070	0.908	0.361	1.143	0.253
0.1	0.550	0.694	0.730	1.007	0.978	0.371	1.322	0.048	1.801	0.032
0.2	0.857	2.502	1.161	1.990	1.574	1.133	2.135	1.499	2.895	0.350
0.3	1.855	2.451	2.417	2.888	3.239	0.376	4.452	1.122	6.268	0.276
0.4	2.794	1.624	3.802	2.148	5.095	0.739	6.732	0.159	8.774	0.091
0.5	4.754	0.309	5.997	0.829	7.709	0.823	10.083	0.340	13.404	0.052
0.6	7.446	0.600	9.315	0.338	11.788	2.209	15.077	1.638	19.474	0.373
0.7	10.608	2.280	12.446	3.217	15.224	0.024	19.359	1.436	25.527	0.416
0.8	13.035	0.233	15.655	0.728	19.153	0.796	23.839	0.382	30.151	0.065
0.9	14.594	1.411	17.519	2.416	21.310	1.050	26.239	0.221	32.676	0.149
1.0	15.919	1.605	19.506	2.024	23.700	0.500	28.567	1.412	34.175	0.472

In all cases, the DR of the data calculated with respect to the experimental data is less than 7%. which indicates that the three models predict the solubility of SD in (methanol + water) cosolvent mixtures with good precision. When graphing the experimental data *vs.* the calculated data (figures 2, 3 y 4), linear holdings are obtained with correlation coefficients equal to 0.99, corroborating that these models show good agreement with the experimental solubility data.

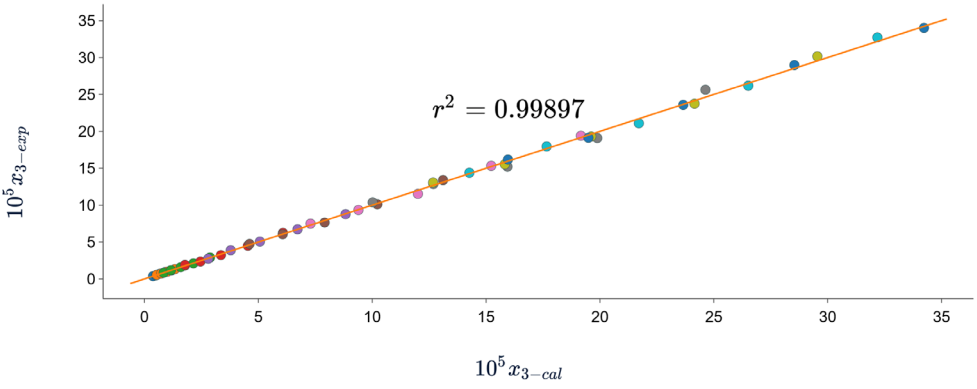

Figure 2. Experimental solubility *vs* calculated solubility by λh model of sulfadiazine in (methanol + water) mixtures.

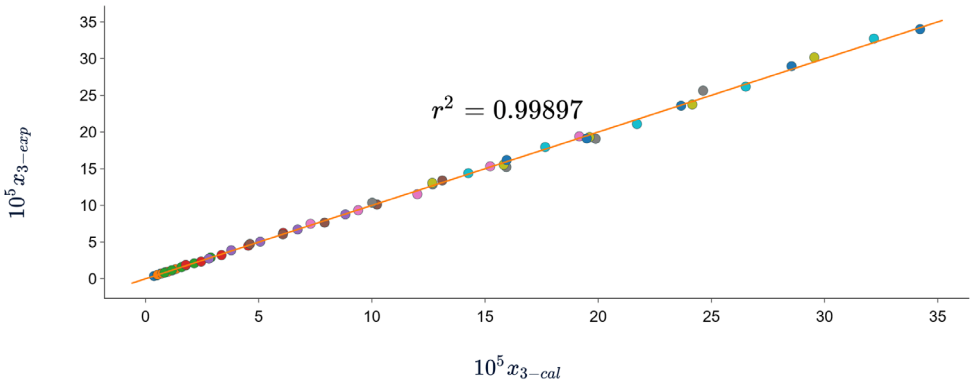

Figure 3. Experimental solubility *vs* calculated solubility by van't Hoff model of sulfadiazine in (methanol + water) mixtures.

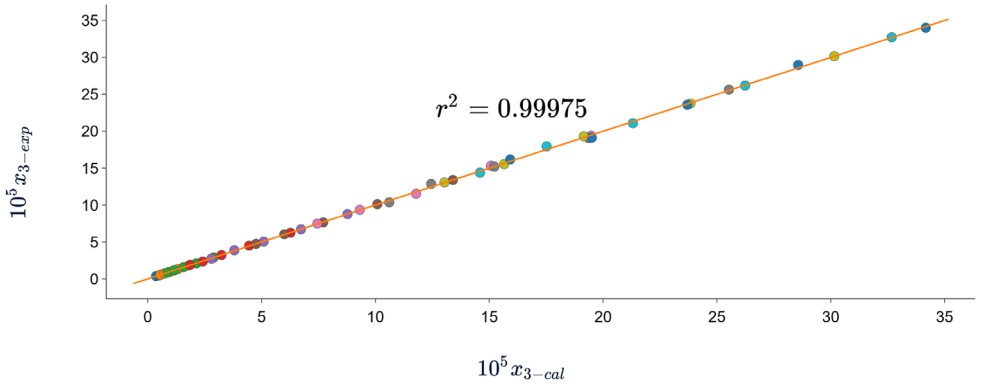

Figure 4. Experimental solubility *vs* calculated solubility by Apelblat model of sulfadiazine in (methanol + water) mixtures.

Table 3 shows the parameters of the equations of λh, van't Hoff and Apelblat, for the solubility of SD in (ethanol + water) cosolvent mixtures and table 4 shows the calculated solubility using each of the exposed models, and the relative deviation. As in the (methanol + water) cosolvent mixtures, the three models predict the solubility data of the SD, with good precision, in this case, the DR are less than 5%.

Table 3. The λh, van't Hoff and Apelblat equations parameters for sulfadiazine in (ethanol + water) cosolvent mixtures.

w_1	λh		van't Hoff		Apelblat		
	λ	h	a	b	A	B	C
0.0	0.012	452082.860	-5242.737	5.390	713.032	-37197.056	-105.387
0.1	0.017	298576.937	-5212.287	5.742	-48.821	-2742.779	8.123
0.2	0.052	105393.552	-5505.28	7.387	-459.017	15545.968	69.466
0.3	0.083	64173.623	-5324.945	7.512	-363.930	11469.983	55.305
0.4	0.041	108496.176	-4467.030	5.208	-203.729	4971.161	31.114
0.5	0.033	120784.624	-4031.583	4.188	-266.243	8182.280	40.273
0.6	0.035	110275.998	-3904.101	4.011	-190.160	4868.094	28.915
0.7	0.042	91475.436	-3893.641	4.175	312.345	-17810.217	-45.894
0.8	0.042	92808.419	-3869.417	4.110	-118.671	1681.403	18.282
0.9	0.031	123363.288	-3815.112	3.710	257.067	-15252.485	-37.734
1.0	0.016	220875.617	-3652.567	2.785	193.870	-12282.134	-28.457

Table 4. Calculated solubility of sulfadiazine in (ethanol + water) mixtures expressed in mole fraction ($10^4 x_3$), from equations of λh, van't Hoff and Apelblat.

	Buchowski–Ksiazaczak λh equation									
w_1	293.15 K	RD	298.15 K	RD	303.15 K	RD	308.15 K	RD	313.15 K	RD
0.0	0.375	1.341	0.506	5.196	0.676	4.771	0.895	1.736	1.175	2.948
0.1	0.592	0.462	0.797	1.131	1.063	1.363	1.405	1.017	1.841	0.305
0.2	1.128	4.139	1.545	2.761	2.095	3.675	2.814	0.790	3.742	1.354
0.3	2.364	0.262	3.205	0.558	4.303	0.203	5.722	2.533	7.541	1.481
0.4	4.406	0.515	5.687	1.153	7.281	2.692	9.248	0.449	11.658	0.544
0.5	7.022	0.893	8.841	0.464	11.048	2.141	13.710	0.087	16.898	0.855
0.6	9.082	0.400	11.351	0.003	14.086	0.039	17.360	1.221	21.258	0.854
0.7	11.087	0.162	13.849	0.058	17.177	0.968	21.159	2.789	25.896	1.773
0.8	11.285	0.351	14.077	1.180	17.435	0.594	21.449	0.785	26.218	0.540
0.9	9.107	0.090	11.325	1.677	13.985	2.169	17.155	0.429	20.911	1.058

(*Continued*)

Table 4. Calculated solubility of sulfadiazine in (ethanol + water) mixtures expressed in mole fraction ($10^4 x_3$), from equations of λh, van't Hoff and Apelblat.

w_1	**293.15 K**	**RD**	**298.15 K**	**RD**	303.15 K	**RD**	**308.15 K**	**RD**	**313.15 K**	**RD**
1.0	6.284	0.304	7.741	0.023	9.474	0.135	11.521	1.406	13.926	1.008
van't Hoff equation										
0.0	0.375	1.344	0.506	5.199	0.676	4.766	0.895	1.735	1.175	2.940
0.1	0.591	0.467	0.797	1.133	1.063	1.358	1.405	1.020	1.841	0.310
0.2	1.128	4.145	1.545	2.761	2.096	3.679	2.814	0.786	3.742	1.355
0.3	2.364	0.267	3.205	0.557	4.303	0.199	5.722	2.536	7.540	1.483
0.4	4.405	0.528	5.688	1.150	7.282	2.702	9.249	0.442	11.657	0.551
0.5	7.020	0.915	8.841	0.460	11.050	2.157	13.711	0.099	16.897	0.865
0.6	9.080	0.422	11.352	0.003	14.088	0.056	17.362	1.233	21.255	0.867
0.7	11.085	0.148	13.851	0.049	17.180	0.985	21.160	2.781	25.891	1.752
0.8	11.283	0.330	14.078	1.174	17.439	0.612	21.451	0.797	26.214	0.555
0.9	9.105	0.105	11.326	1.688	13.988	2.151	17.156	0.421	20.906	1.034
1.0	6.282	0.285	7.742	0.012	9.476	0.157	11.522	1.395	13.923	0.982
Apelblat equation										
0.0	0.363	4.561	0.513	6.566	0.695	2.070	0.908	0.361	1.143	0.253
0.1	0.550	0.694	0.730	1.007	0.978	0.371	1.322	0.048	1.801	0.032
0.2	0.857	2.502	1.161	1.990	1.574	1.133	2.135	1.499	2.895	0.350
0.3	1.855	2.451	2.417	2.888	3.239	0.376	4.452	1.122	6.268	0.276
0.4	2.794	1.624	3.802	2.148	5.095	0.739	6.732	0.159	8.774	0.091
0.5	4.754	0.309	5.997	0.829	7.709	0.823	10.083	0.340	13.404	0.052
0.6	7.446	0.600	9.315	0.338	11.788	2.209	15.077	1.638	19.474	0.373
0.7	10.608	2.280	12.446	3.217	15.224	0.024	19.359	1.436	25.527	0.416
0.8	13.035	0.233	15.655	0.728	19.153	0.796	23.839	0.382	30.151	0.065
0.9	14.594	1.411	17.519	2.416	21.310	1.050	26.239	0.221	32.676	0.149
1.0	15.919	1.605	19.506	2.024	23.700	0.500	28.567	1.412	34.175	0.472

Figures 5, 6 and 7 show the correlation between the experimental solubility data of SD in (ethanol + water) cosolvent mixtures and those calculated with the three models, in all cases the correlation coefficients are equal to or greater than 0.99.

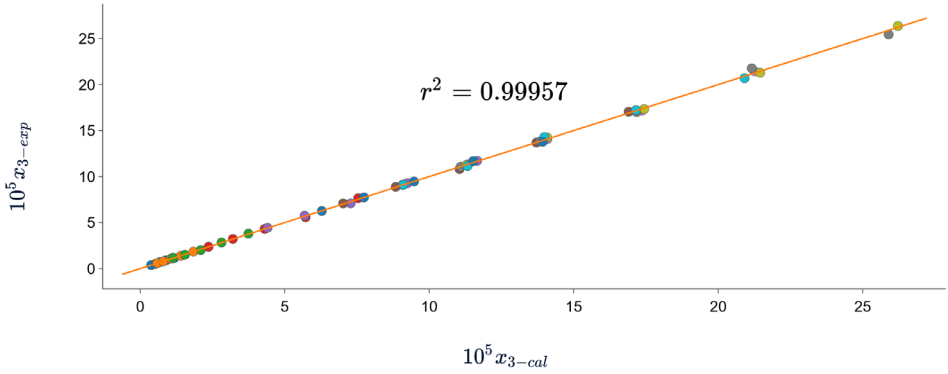

Figure 5. Experimental solubility *vs* calculated solubility by λh model of sulfadiazine in (ethanol + water) mixtures.

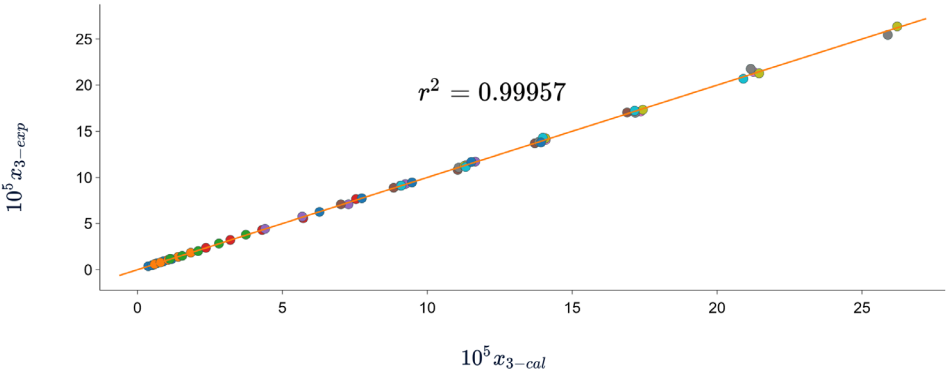

Figure 6. Experimental solubility *vs* calculated solubility by van't Hoff model of sulfadiazine in (ethanol + water) mixtures.

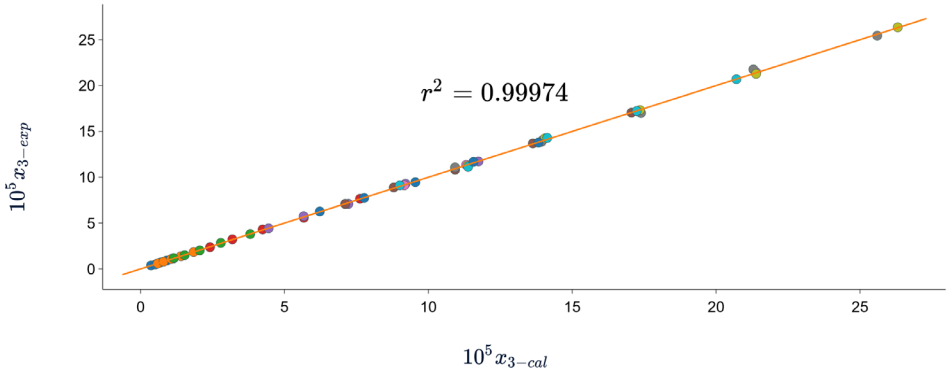

Figure 7. Experimental solubility *vs* calculated solubility by Apelblat model of sulfadiazine in (ethanol + water) mixtures.

Table 5 shows the parameters of the equations of λh, van't Hoff and Apelblat, for the solubility of SD in (1-propanol + water) cosolvent mixtures and table 6 shows the calculated solubility using each of the exposed models, and the relative deviation.

Table 5. The regression parameters of the Apelblat, van't Hoff, and λh model for sulfadiazine in (1-propanol + water) mixtures.

w_1	λh		van't Hoff		Apelblat		
	λ	h	a	b	A	B	C
0.0	0.012	451771.183	-5243.218	5.392	712.964	-37194.385	-105.377
0.1	0.016	314684.946	-4894.286	5.032	371.415	-21443.827	-54.561
0.2	0.022	214826.896	-4760.884	5.136	94.695	-8770.827	-13.357
0.3	0.043	107306.471	-4636.504	5.572	373.823	-21276.670	-54.836
0.4	0.055	83741.522	-4605.045	5.754	-172.781	3454.943	26.590
0.5	0.067	67398.827	-4537.686	5.831	-69.720	-1123.467	11.250
0.6	0.074	59687.244	-4436.373	5.741	166.048	-11686.808	-23.867
0.7	0.056	73997.588	-4171.041	4.970	-39.879	-2132.985	6.672
0.8	0.045	88738.406	-3996.161	4.422	-175.520	4134.765	26.795
0.9	0.029	132531.458	-3874.517	3.764	165.295	-11166.077	-24.058
1.0	0.016	248491.514	-3949.778	3.296	-427.185	15494.320	64.107

Table 6. Calculated solubility of sulfadiazine in (1-propanol + water) mixtures expressed in mole fraction ($10^4 x_3$), from equations of λh, van't Hoff and Apelblat.

	Buchowski–Ksiazaczak λh equation									
w_1	293.15 K	RD	298.15 K	RD	303.15 K	RD	308.15 K	RD	313.15 K	RD
0.0	0.375	1.342	0.506	5.197	0.676	4.770	0.895	1.736	1.175	2.948
0.1	0.860	0.856	1.138	0.643	1.491	0.373	1.938	2.213	2.498	1.678
0.2	1.505	1.653	1.976	1.035	2.572	3.044	3.318	2.431	4.247	0.091
0.3	3.556	0.135	4.635	0.915	5.990	0.090	7.678	2.591	9.764	1.774
0.4	4.753	1.420	6.184	1.561	7.978	0.055	10.208	0.461	12.961	0.645
0.5	6.455	2.143	8.368	3.534	10.754	1.629	13.711	0.533	17.348	0.214
0.6	8.334	1.577	10.740	2.261	13.726	0.651	17.406	2.347	21.908	1.072
0.7	9.537	0.496	12.105	1.541	15.245	2.492	19.059	1.882	23.662	0.382

(*Continued*)

Table 6. Calculated solubility of sulfadiazine in (1-propanol + water) mixtures expressed in mole fraction ($10^4 x_3$), from equations of λh, van't Hoff and Apelblat.

Buchowski–Ksiazaczak λh equation										
w_1	**293.15 K**	**RD**	**298.15 K**	**RD**	303.15 K	**RD**	**308.15 K**	**RD**	**313.15 K**	**RD**
0.8	10.006	1.358	12.573	1.946	15.681	1.178	19.422	1.384	23.896	0.761
0.9	7.849	1.704	9.795	3.547	12.135	1.733	14.933	1.002	18.258	0.980
1.0	3.801	1.935	4.764	1.137	5.926	0.934	7.321	1.486	8.986	1.596
van't Hoff equation										
0.0	0.375	1.344	0.506	5.200	0.676	4.766	0.895	1.735	1.175	2.940
0.1	0.860	0.851	1.138	0.640	1.492	0.380	1.938	2.210	2.498	1.669
0.2	1.505	1.648	1.976	1.031	2.572	3.037	3.318	2.435	4.247	0.082
0.3	3.555	0.142	4.635	0.919	5.991	0.098	7.678	2.587	9.763	1.764
0.4	4.752	1.431	6.184	1.563	7.979	0.064	10.209	0.468	12.960	0.651
0.5	6.455	2.154	8.368	3.537	10.755	1.620	13.712	0.539	17.347	0.221
0.6	8.333	1.587	10.740	2.265	13.728	0.661	17.407	2.341	21.906	1.063
0.7	9.536	0.510	12.105	1.546	15.247	2.479	19.061	1.890	23.659	0.394
0.8	10.004	1.378	12.573	1.951	15.684	1.162	19.424	1.395	23.893	0.772
0.9	7.848	1.721	9.795	3.556	12.137	1.716	14.934	0.993	18.254	0.960
1.0	3.800	1.962	4.764	1.140	5.927	0.952	7.322	1.500	8.985	1.603
Apelblat equation										
0.0	0.363	4.536	0.512	6.551	0.695	2.086	0.908	0.343	1.144	0.248
0.1	0.845	0.911	1.145	0.006	1.513	1.841	1.953	1.455	2.465	0.356
0.2	1.507	1.769	1.986	0.566	2.583	2.612	3.320	2.485	4.218	0.589
0.3	3.490	1.992	4.662	1.508	6.077	1.546	7.739	1.810	9.642	0.504
0.4	4.789	0.662	6.162	1.196	7.921	0.661	10.171	0.097	13.046	0.013
0.5	6.479	1.787	8.357	3.401	10.722	1.923	13.688	0.360	17.388	0.016
0.6	8.256	2.490	10.761	2.460	13.811	1.272	17.471	1.981	21.801	0.579
0.7	9.573	0.116	12.108	1.567	15.223	2.633	19.032	1.735	23.666	0.367
0.8	10.094	0.492	12.535	1.642	15.571	1.871	19.345	0.984	24.035	0.183
0.9	7.793	2.416	9.826	3.882	12.215	1.084	14.981	0.683	18.140	0.327
1.0	3.878	0.039	4.726	0.341	5.825	0.789	7.254	0.551	9.121	0.120

According to the results shown in table 6 and figures 8, 9 and 10, in which the experimental and calculated solubility are compared. the three solubility models, including Apelblat model, Buchowski-Ksiazaczak λh equation and van't Hoff model, were applied to fit with experimental data obtaining a good predictability of the experimental data, since the DR values do not exceed 5%.

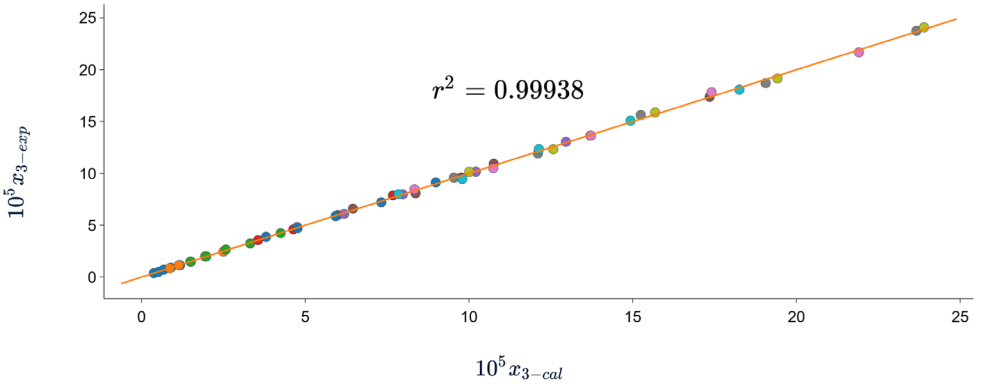

Figure 8. Experimental solubility *vs* calculated solubility by λh model of sulfadiazine in (1-propanol + water mixtures) mixtures.

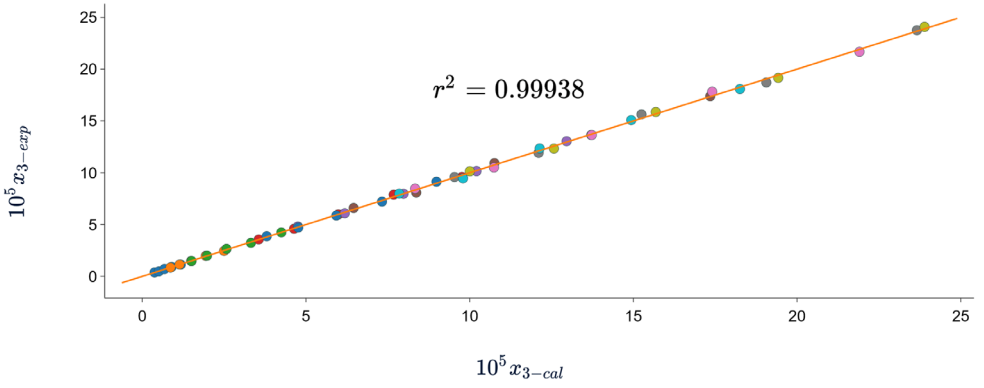

Figure 9. Experimental solubility *vs* calculated solubility by van't Hoff model of sulfadiazine in (1-propanol+ water) mixtures.

In general terms, from the results shown in tables 2, 4, 6 and figures 2-10, it can be observed that the Apelblat model, Buchowski-Ksiazaczak λh equation and van't Hoff model gave almost the same goodness of fit to the experimental data. Error percentages of the predicted solubility values obtained from calculations using both models were below 5%, except for one point of SD solubility in (methanol + water) mixtures

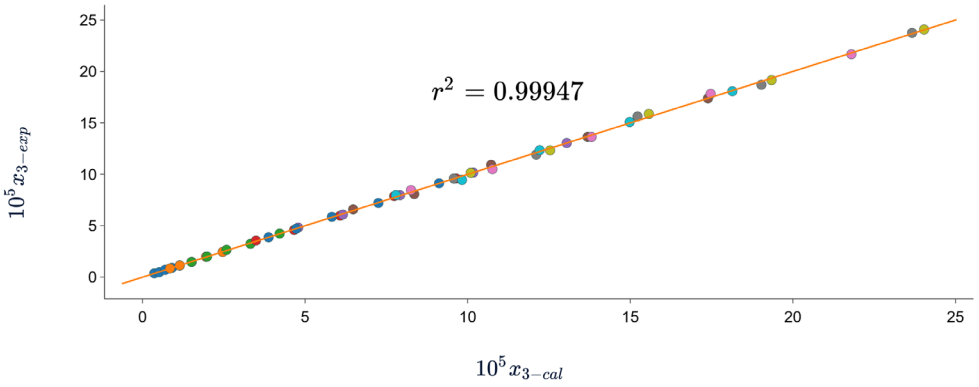

Figure 10. Experimental solubility *vs* calculated solubility by Apelblat model of sulfadiazine in (1-propanol+ water) mixtures.

(w_3 at 293.15 K). The goodness of fit of these equations can also be seen from the r^2 values listed in figures 2-10, which are almost unity. Buchowski *et al.* [38] stated that in an ideal solution, the value of λ equals to 1. The values of the obtained equation parameter (λ) in tables 2, 4 and 6 showed that the SD in (methanol + water), (ethanol + water) and (1-propanol + water) cosolvent mixtures, understandably were nonideal. This agrees with Delgado and Martínez [6-8], who reported that solution of SD in some cosolvent mixtures are highly non-ideal.

Acknowledgements

The authors gratefully acknowledge support from the Faculty of Science and Humanities and Research Direction of the Fundación Universidad de América.

Disclosure statement

No potential conflict of interest was reported by the authors.

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How to cite this article

R.E. Cardenas, L.E. Tinoco, D.M. Galindres, A. Beltrán, C.D. Oviedo, J. Osorio, Prediction of sulfadiazine solubility in some cosolvent mixtures using non-ideal solution models, *Rev. Colomb. Cienc. Quím. Farm.*, **49**(3), 822-842 (2020).

Rev. Colomb. Cienc. Quím. Farm., Vol. 49, números 1 a 3, 2020.

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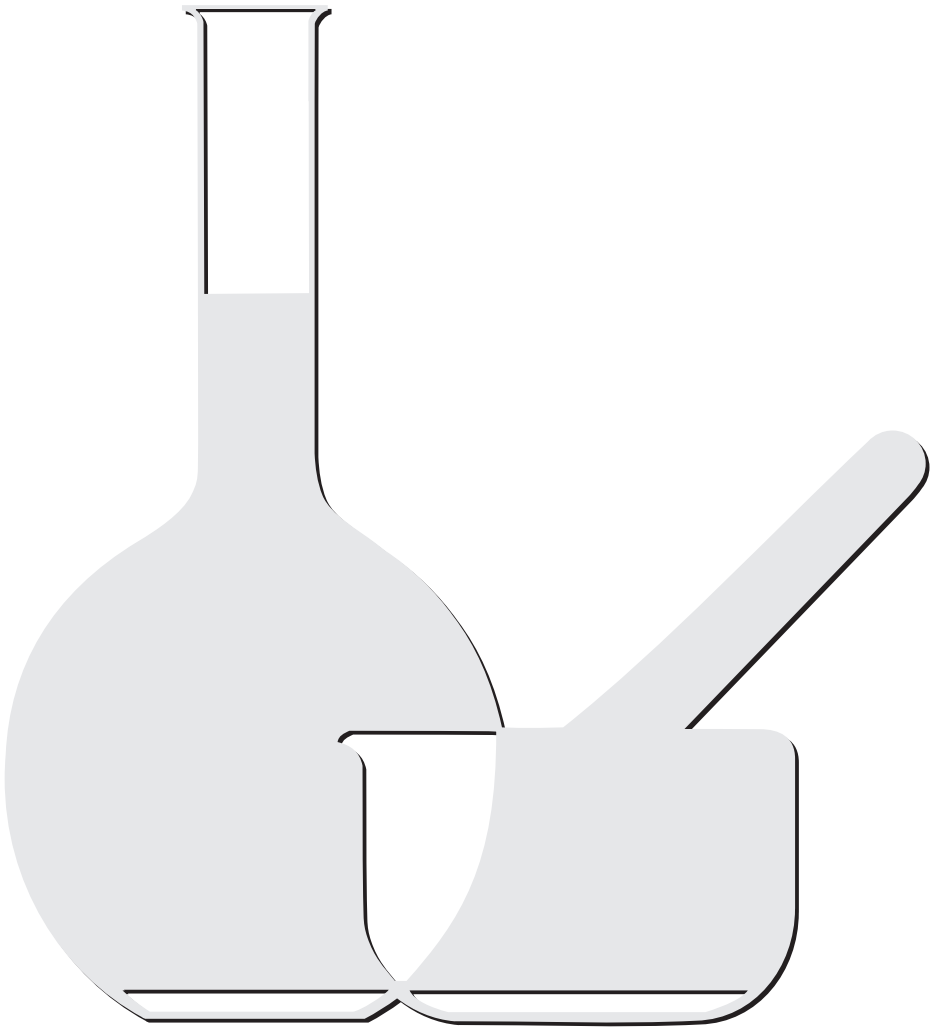

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UV λ max (solvente ε) nm (log ε). Ej.: UV λ max (MeOH) 275 (log ε 2,94).

IR ν max (medio) cm^{-1}. Ej.: IR ν max (KBr) 1740, 1720 cm^{-1}.

EM *m/z* (% intensidad relativa). Ej.: em *m/z* (%): 340 (M^+, 100), 295 (10), 134 (26) ...

RMN ^1H (solvente, frecuencia de registro) δ ppm (integración, multiplicidad, J en Hz, asignación). Ej.: RMN ^1H ($CDCl_3$, 400 MHz) 3,84 (1H, *d*, J = 10,3 Hz, H-30).

RMN ^{13}C (solvente, frecuencia de registro) δ ppm (multiplicidad, asignación). Ej.: RMN ^{13}C ($CDCl_3$, 600 MHz) 16,60 (t, C-12).

Las abreviaturas usadas para describir la multiplicidad de las señales en RMN son: *s* = singlete, *d* = doblete, *t* = triplete, *m* = multiplete, *dd* = doble de dobletes, *ddd* = doble de doble de dobletes.

Las abreviaturas para los solventes y reactivos más comúnmente usados son: EtOH= etanol, MeOH = metanol, $CHCl_3$ = cloroformo, C_6H_6 = benceno, AcOEt = acetato de etilo, EP = éter de petróleo, Me_2CO = acetona, DMSO = dimetilsulfóxido, AcOH = ácido acético.

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Revista Colombiana de Ciencias Químico-Farmacéuticas
Departamento de Farmacia
Facultad de Ciencias
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Dirección WEB:
http://www.revistas.unal.edu.co/index.php/rccquifa

Revista Colombiana
de Ciencias Químico-Farmacéuticas, 49(3)
se terminó de editar, imprimir y encuadernar
en Proceditor, sobre papel bond de 90 gramos
Bogotá, D. C., Colombia.