Preparation and in-Vitro Evaluation of Cinnarizine Raft Forming Chewable Tablets

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Abstract:

Cinnarizine is an anti-histaminic drug and is mainly used to treat symptoms accompanying motion sickness like vomiting and dizziness. It has low and variable bioavailability due to its low water solubility. Cinnarizine (weakly basic drug) is formulated as raft forming chewable Tablets to allow its complete dissolution at the stomach to be absorbed at the upper part of small intestine. Raft forming chewable Tablets are formulated by direct compression method using sodium alginate or pectin as raft forming agents. The prepared Tablets were evaluated for their pre and post- compression parameters and they have shown desirable results regarding evaluation of hardness, thickness, % friability, weight variation, content uniformity, raft strength, weight and volume, in addition to in-vitro drug release. Out of all the prepared formulas F1 selected as the optimum formula with 488.1mg raft strength and 92.34% drug release after 24hrs that is promising for the formulation of the raft system.

Key words: raft, gastro-retentive, cinnarizine, sodium alginate, chewable Tablets.

التحضير والتقييم المختبري لأقراص السنارزين القابلة للمضغ المشكلة للطوف

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الخلاصة:

السنارزين هو دواء مضاد للهستامين ويستخدم أساسا لعلاج الاعراض المصاحبة لدوار الحركة والتي تشمل التقيؤ والشعور بالدوران وعدم الاتزان. هذا الدواء يتميز بقلة توافره الحيوي في الدم بسبب قلة ذوبانيته في الماء. السنارزين (دواء قاعدي ضعيف) تم صياغته على شكل حبوب مكونة للطوف قابلة للمضغ في الفم لمنحه الفرصة لكي يذوب بالكامل في المعدة ليتم امتصاصه في الجزء الأعلى من الأمعاء الدقيقة. الحبوب المكونة للطوف تمت صياغتها بطريقة الكبس المباشر باستخدام الجينات الصوديوم او البكتين وهما العاملان الاساسيان في تكون الطوف. الحبوب المحضرة تم تقييمها مختبريا قبل وبعد الكبس لعدة متغيرات ولقد أعطت نتائج مرضية لعديد من الفحوصات مثل قياس الصلابة، قياس السمك، الوزن المتغير، المحتوى الدوائي وتحرر الدواء. من بين جميع الصيغ المحضرة الصيغة الأولى هي المختارة كأفضل صيغة والتي تملك قوة الطوف التي تقدر ب ٤٨٨,١ ملغ وما يقارب ٩٢٪ ذوبانية دواء بعد ٢٤ ساعة ولديها صفات جيدة لتحضير الحبوب المشكلة للطوف.

الكلمات المفتاحية: طوف،سنارزين،متبقي في المعدة، الجينات الصوديوم،حبوب قابلة للمضغ

Introduction

Classical oral drug delivery systems are the most widely used in pharmaceutical domain to cure diseases. However, oral route of drug administration includes many obstacles such as, non-site specificity. In

certain cases, some drugs are needed to be released and absorbed at particular site [1]. Another obstacle is the GI transit time, gastric emptying is extremely fickle and is dependent on many elements, drugs having a short half-life are eliminated quickly from the blood circulation [2].

This has led to the development of non-classical oral drug delivery system such as gastro-retentive drug delivery system (GRDDS) to overcome the mentioned problems [3].

GRDDS have many advantages such as reducing mucosal irritation through controlling the release of the drug and prevent local high drug concentration in stomach, provide adequate local therapeutic scale and limit the systemic exposition to the drug and improve its bioavailability [4].

One of the GRDDS is the raft forming system, general mechanism includes a rapid reaction between acidic content of the stomach and the raft forming agents of this system that lead to the formation of a viscous cohesive gel floats over the gastric content by the aid of gas generating agents that liberates CO_2 gas [5]. Raft floating usually takes few seconds after the dose administration and during the floating period, the drug is released in a slower desired rate from the system. After complete release of the drug, the residual system is emptied from the stomach [6].

Cinnarizine is an anti-histaminic drug and is mainly used for treatment of symptoms of motion sickness like vomiting and dizziness, and it is also useful for vestibular symptoms of other origins [7]. It is practically insoluble in water, soluble in dilute HCl, it has log P of 5.8 and pKa 8.4 and it is considered as weak base [8].

The aim of this study is to formulate and evaluate a chewable raft forming Tablet containing cinnarizine to be used as a once daily prolonged release dosage form for cinnarizine thus increase patient compliance.

Materials and methods:

Materials:

Cinnarizine was supplied from Baoji Guokang Bio-Technology Co., Ltd (china), sodium alginate and pectin were obtained from Jiangsu yew pharmaceutical co., ltd (India), PVP K30M was gained from Samara drug industry (Iraq) and all other ingredients used to formulate the chewable Tablets were obtained from Provizer pharma (India). All the materials were used as received.

Methods:

Formulation of cinnarizine raft forming chewable Tablets:

Raft forming chewable Tablets were prepared by direct compression using six different formulations shown in Table (1). Accurately weighted amount of the ingredients (the drug, raft forming agent, diluent, binder and gas generating agent) were mixed for 10 minutes and sieved through a (no.45) sieve to achieve uniform mixture of powder blend, then weighted amount of talc and magnesium stearate was added to the powder blend and mixed for around 5 minutes then compressed by mini press Tablet machine utilizing a 11mm biconcave punch [9].

Table (1): Composition of different formulations of cinnarizine raft forming Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Sodium alginate	100	120	150	-	-	-
Pectin	-	-	-	100	120	150
Sodium bicarbonate	30	30	30	30	30	30
Calcium carbonate	100	100	100	100	100	100
PVP K30M	40	40	40	40	40	40
Mannitol	238	218	188	238	218	188
Sodium saccharin	2	2	2	2	2	2
Mg stearate	10	10	10	10	10	10
Talc	5	5	5	5	5	5
Cinnarizine	75	75	75	75	75	75
Total weight	600	600	600	600	600	600

Evaluation parameters:

Pre-compression parameters:

To determine the flow of powders during formulation the following parameters was measured including angle of repose, bulk density, tapped density, carr's index and hausner ratio.

Post compression evaluation:

Thickness test:

The thickness of the Tablets was measured by the use of Vernier caliper. Three Tablets from each formula were chosen and measured, then the mean value was calculated ± SD [10].

Hardness test

The hardness of the Tablets in the unit (Kg/cm2) was measured by the use of the manual hardness tester. Three Tablets from each formula were chosen and measured, then the mean value was calculated ± SD (11).

Weight variation

The weight variation test was achieved by weighing twenty of the rafts forming chewable Tablets separately, then average weight of the Tablets was calculated and compared the weight of every Tablet to the calculated average weight [12].

Friability

Friability test was achieved by weighing twenty Tablets and placing them in the friabilator, then the device was set up at 25 rpm for four minutes. After that the Tablets were de-dusted and weighed again. The %friability was calculated by applying the following equation [13]:

$$\%\ \text{Friability} = \left[\frac{\text{initial weight} - \text{final weight}}{\text{initial weight}}\right] * 100$$

Content uniformity

Twenty of the prepared Tablets were weighed and triturated in a mortar. An amount of powder equivalent to 75mg Cinnarizine was precisely weighed and transferred into 10 mL volumetric flask and 10 mL of 0.1 N HCL was added to the volumetric flask and shaken thoroughly. Filtration of the resulting solution was done with 0.45µ membrane filter, and 1 mL of the filtrate was transferred to 100 mL volumetric flask and diluted up to 100 mL with 0.1 N HCl and measured the absorbance of the resulting solution by

UV-visible spectrophotometer at λ_{max} of the drug [14].

Floating lag time and raft formation duration:

Floating lag time for the raft was performed by using a magnetic stirrer adjusted at 37°C and 100 rpm then a prepared raft forming chewable Tablet was crushed in a mortar and added to a 200mL of 0.1 N HCl in a 250 mL beaker. The time between introducing the crushed Tablet into the solution and until the whole crushed Tablet rise on the surface and no insoluble particles sank on the bottom is called the floating lag time. After the raft formed, the beaker was removed from the magnetic stirrer and set aside to check the raft perfection and duration [15].

Raft strength measurement:

Raft strength measurement was performed using a modified method from that reported in literatures, using a double pan balance. The powdered Tablet was added to 150 mL of 0.1 N HCL in a 250 mL glass beaker which was maintained at 37°C. On the left pan 250mL beaker containing 150 mL HCl solution (37°C) was placed and on the right pan, 250 mL beaker containing water was placed. L-shaped wire probe (1.2mm diameter) was introduced (just below the surface of the HCl solution) into the left side beaker and was held up during the experiment. To the beaker containing HCl solution the crushed Tablet was added and allowed the raft to form on the surface. Then water was withdrawn from the beaker (placed on the right pan) gradually using plastic dropper until the L-shaped wire moved up and the weight of the withdrawn water was measured, and this will represent the raft strength in the units of mg [16]. The assembly used for raft strength measurement is shown in Figure (1).

Figure (1): Double pan balance and the wire probe used for raft strength measurement (modified method).

Raft weight:

The crushed Tablet was place in a graduated beaker containing 125 mL of 0.1 N HCl and allowed to form the raft and left to settle for about few minutes, then the weight of the raft was measured by applying the following equation (17):

Raft weight= W2-W1

In which W1 is the weight of the beaker containing 125mL of 0.1N HCl before the addition of the Tablet

W2 is the weight of the beaker after the addition of the crushed Tablet.

Raft volume:

Raft volume measurements was performed using the following steps [17].

The volume of the beaker before raft formation (V1).

1.After 30 minutes, the position to which each raft reached at the top was marked from the outside of the beaker.

2.The beaker content was removed, dried with a paper towel and refilled with 0.1N HCl up to the previously marked position

and the volume of added 0.1N HCl was measured (V2).
3.The raft volume was calculated using the equation: Raft volume= V2-V1

In-vitro dissolution study:

In-vitro dissolution study of cinnarizine raft forming chewable Tablets was performed by using USP type II apparatus (paddle type) adjusted at 37±0.5°C in 900ml HCl solution pH 1.2 at 50 rpm Tablets was crushed and added to the jar of dissolution apparatus. 5 mL samples were withdrawn at specific time intervals at (0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 20 and 24 hrs) and substituted with fresh medium. Then each sample was filtered by Millipore filter 0.45 µ membrane and properly diluted and measured by UV-visible spectrophotometer at λ max. Each sample was performed in triplicate (18).

Drug-excipient compatibility studies:

The compatibility between cinnarizine and excipients used in the formulation of the raft Tablets were tested by Fourier transform infrared spectroscopy (FTIR). The pure cinnarizine powder, the powder of crushed Tablet of the selected formula (F1) and physical mixture for the F1 were tested individually according to KBr method by mixing approximately 1mg of sample with 200mg KBr in mortar and the mixture was compressed using hydraulic press into disc before spectra analysis for each sample from 4000-400 cm-1 (19).

Statistical analysis: All the data were given as mean ± SD. Statistical analysis was carried out by applying GraphPad Prism Version 7 by choosing one-way ANOVA, then Tukey's test (pairwise comparisons) at 95% significance difference ($p<0.05$).

Results and discussion:

Pre-compression evaluations:

The measured values for angle of repose, bulk density, tapped density, carr's index and hausner ratio with their corresponding flow character for each formula of the prepared powder mixture are stated in Table (4).

Table (4): The results of flowability evaluation

Formula Number	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Flow character
F1	31.35±2.1	0.321±0.02	0.401±0.02	11.15±0.99	1.12±0.08	Good
F2	34.41±2.3	0.301±0.01	0.427±0.02	14.32±1.23	1.15±0.07	Good
F3	33.55±1.8	0.352±0.01	0.45±0.03	14.05±0.87	1.16±0.05	Good
F4	33.1±2.9	0.331±0.03	0.443±0.01	14.9±1.16	1.16±0.05	Good
F5	37.11±1.2	0.34±0.01	0.371±0.04	19.1±0.81	1.19±0.11	Fair
F6	37.8±1.3	0.35±0.02	0.356±0.02	17.33±1.34	1.20±0.07	Fair

Data represent mean ±SD, n=3

The angle of repose of all the prepared formulas was between 31.35°-37.8°, the results of the carr's index and hausner ratio was between 11.15%-19.1% and 1.12-1.2 respectively. The results indicated that the prepared powder mixtures have accepTable flow properties and compressibility.

Post compression evaluations:

The results of post compression evaluation test results are presented in Table (5).

Table (5): Post compression evaluation of cinnarizine raft forming chewable Tablets

Formula number	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Content uniformity (%)
F1	6.21±0.006	4.18±0.06	595.1±0.87	0.983	95.7±1.7
F2	6.25±0.011	3.25±0.11	599.1±1.3	0.668	96.1±1.9
F3	6.22±0.023	3.39±0.23	599.9±1.7	0.785	96.7±2.3
F4	6.23±0.007	4.11±0.21	596.3±0.95	0.911	98.9±4.5
F5	6.23±0.025	4.22±0.025	600.1±1.8	0.467	98.1±3.6
F6	6.29±0.047	3.78±0.17	600.2±1.7	0.671	95.5±4.1

Data represent mean ±SD, n=3

The thickness of the prepared cinnarizine chewable Tablets measured were in the range of (6.21mm±0.006 to 6.29mm ±0.047) that indicates a uniform thickness.

The hardness of the prepared cinnarizine chewable Tablets were in the range of (3.25 kg/cm^2±0.11 to 4.22 kg/cm^2±0.025) indicating a good mechanical strength that is sufficient for chewable Tablets [21].

The weight variation test according to USP criteria if no more than two of the prepared Tablets exceeded the limit ratio and if no Tablet varies by double the percentage limit then the prepared Tablets were accepted [19].

The weight variation of the prepared cinnarizine raft forming chewable Tablets was ranging from (595.1±0.87 to 600.2 ±1.7), in which none of the Tablets was exceeding the limit of (±5% i.e. 630-570mg) specified by the USP [20].

The allowable weight loss percentage (% friability) should be less than 1%. The total weight loss of the prepared raft forming chewable Tablets after the friability test was in the rage from (0.467% to 0.983%), which is less than 1%.

The content uniformity values for the prepared chewable Tablets was in the range of (95.5±4.1 to 98.9±4.5) that reveals a proper dose and uniform distribution of the active ingredient and a good content uniformity in which no Tablet lie out of the range (85%_115%) [22].

Raft formation lag time and duration:

Raft formation floating lag time for all the prepared cinnarizine chewable Tablets are illustrated in Table (7).

Table (7): Floating lag time of the prepared raft forming Tablets

Formula number	Floating lag time (minute)	Floating duration (hrs.)
F1	2±1.78	>24
F2	3±1.11	>24
F3	3.5±0.98	>24

The results were in the range of 1 minute to 3.5 minutes for complete raft formation and floatation. All the formulas (except F4, F5 and F6) had rapid floating lag time due to the presence of gas generating agent in the composition of all formulations. This agent when comes in contact with the acidic dissolution media (HCl solution pH 1.2), it generates carbon dioxide and consequently becomes entrapped within the gelling layer of the hydrophilic polymer. This reduce the density of this gelling layer below that of the surrounding media and thus floats in the form of raft [23].

Tablets prepared using formulations containing pectin only as a raft forming agent (i.e. F4, F5 and F6) did not form a raft on the surface of the dissolution media but only a few dispersible fine particles on the surface as thin layer which did not consider as a raft. It was concluded that the formulas containing pectin in different concentrations (F4, F5, and F6) did not form a raft even after increasing its concentration since pectin did not form a viscous gelling layer [24].

Duration of raft floatation was followed up over the study period and it was recorded that all the formulations that formed a raft over the surface of the acidic media preserved their raft integrity for the 24 hrs study period as shown in Table (7).

Raft strength, weight and volume:

Raft strength, weight and volume values of all the prepared raft forming Tablets are shown in Table (8).

Table (8): Raft strength measurement, raft weight and volume

Formula number	Raft strength (mg)	Raft weight (g)	Raft volume (mL)
F1	488.1±1.77	2.32±1.12	12.12±2.3
F2	490.7±0.87	2.51±1.75	12.97±1.82
F3	510.8±1.82	2.89±0.87	13.20±0.95

Among all formulations formula 3 prepared with highest concentration (150mg) of sodium alginate showed maximum raft strength compared to F1 and F2 (containing 100, 120 mg sodium alginate respectively) due to increase visco-elastic strength of the formed raft since increasing the amount of raft forming agent has a direct relationship with raft strength [25].

Table (8) also shows a direct relation between raft strength and both the weight and volume of the raft for all the tested formulations, as the raft weight and volume increased this led to increase raft

strength and these results agreed with previous reported data [26].

In-vitro release profile:

In-vitro release of cinnarizine from the crushed prepared raft forming Tablets were carried out in 0.1 N HCl solution under sink condition and followed up to 24 hrs and the results are shown in Table (9).

Table (9): Cumulative release of cinnarizine raft forming crushed chewable Tablet

%Cumulative drug release			
Formula number	**After 6h**	**After 12h**	**After 24h**
F1	74.27%	81.68%	92.34%
F2	69.00%	78.51%	88.23%
F3	66.70%	75.14%	86.28%

All the prepared formulas had initial burst effect (about 35%) within 0.5-1hr due to the high solubility of cinnarizine in 0.1N HCl since it is a weakly basic compound, followed by slow release phase that continued up to 24 hrs. This is due to the formation of raft floated on the surface of the dissolution media and the raft is a viscous gel like structure that entrapped the drug within its structure thus provide sustained release profile of the drug over 24hr as shown in Figure (5).

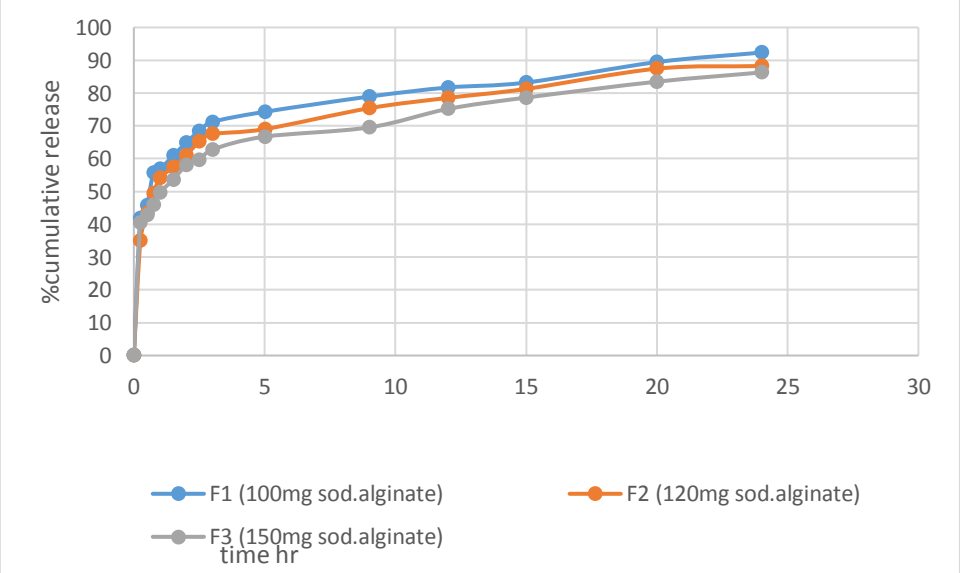

Figure (5): The in-vitro release of cinnarizine from raft forming Tablets in HCl solution pH 1.2 at 37°C

The in-vitro release of cinnarizine from the raft in formula 1, 2 and 3 showed a slight decrease in the drug release with increasing raft forming agent amount as shown in Figure (5), since F3 showed stronger and thicker layer of the raft compared to F1 and F2 leading to minimize cinnarizine release [26].

Sodium alginate 100mg was chosen as the optimum amount of the raft forming agent since it produced accepTable raft properties and almost complete drug release at the end of 24hrs. F1 was chosen as the optimum formulation since it gave raft strength (488.1mg) and drug release (92.3%) after 24hrs.

Drug-excipients compatibility

FTIR spectrum of the pure cinnarizine powder is shown in Figure (6), the Figure shows the following absorbance bands that appears at the frequencies of 2959 cm^{-1} which represents CH stretching of (aromatic, alkene, mono-substituted), 2936 cm^{-1} is the CH stretching of (aliphatic alkane), 1597 cm^{-1} is the C=C stretching of (aromatic ring), 1490 &1448 cm^{-1} represent the CH_2 (alkane stretch), 1134 cm^{-1} for C-N stretching and lastly the bands of 999 & 962 for =CH out of plane (aromatic, alkene stretch) [27].

FTIR spectrum of cinnarizine after formulation in raft forming Tablets displayed the same functional groups band with slight decrease in the intensity that may be due to the dilution with the excipients added to formulations and that indicates compatibility of excipients with the drug as shown in Figure (7).

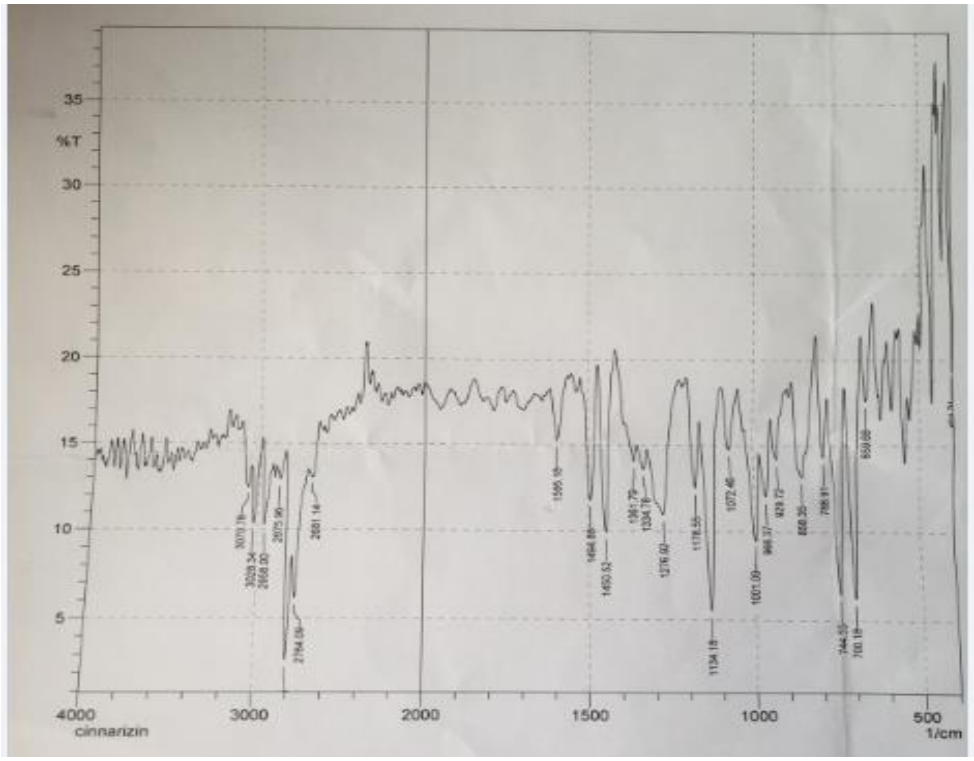

Figure (6): FTIR spectra of cinnarizine pure drug

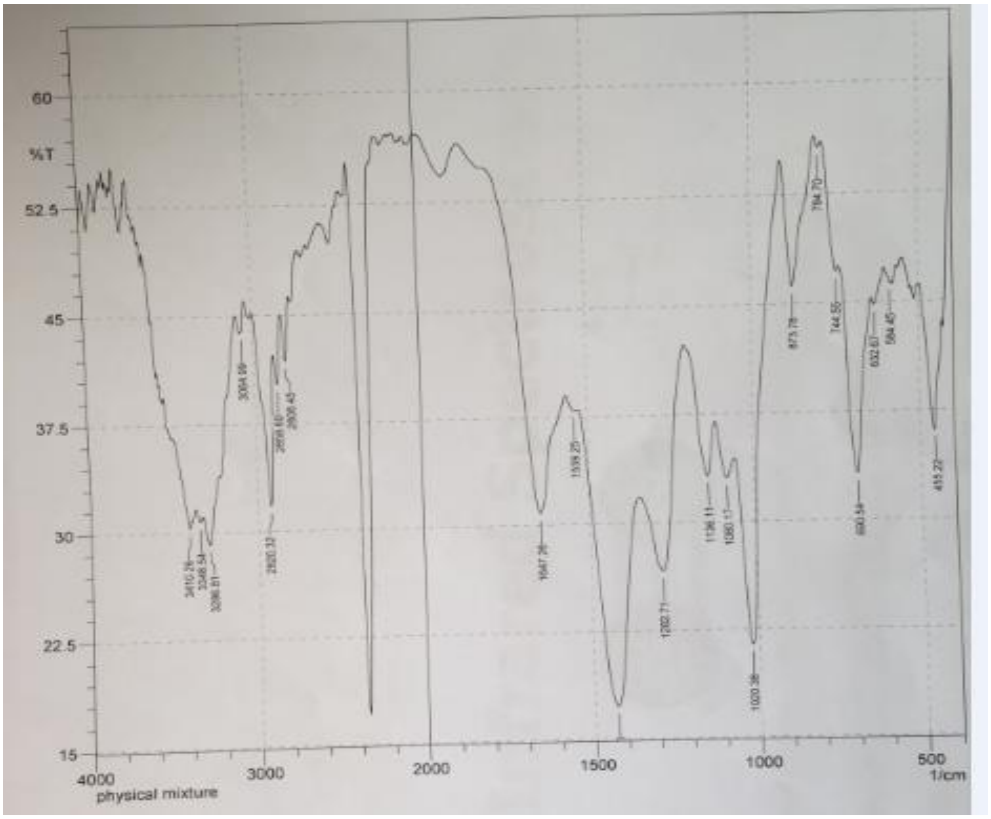

Figure (7): FTIR of the physical mixture of selected formula 1

Conclusion:

Based on the results of this study, it is able to prepare an accepTable chewable raft forming Tablets containing 75mg cinnarizine using raft forming agent (sodium alginate) and a good raft property obtained using lowest amount of sodium alginate (100mg) rather than high amount (150mg).

Initial burst releasing of the drug from the prepared raft forming chewable Tablet followed by a sustained manner of release which has a potential of using this type of Tablets to enhance the dissolution and bioavailability of the drug and reduce the frequency of drug administration from three times daily into once daily. The drug and excipients used in formulation of raft forming Tablet are compatible as the result of FTIR showed.

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