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Optimization, Development and evaluation of Microemulsion for the release of combination of Guaifenesin and Phenylephrine

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ABSTRACT

Guaifenesin and Phenylephrine possess greater water solubility but lower permeability and bioavailability. The aim of this study is to develop a microemulsion to overcome these issues. Castor oil, Oleic acid and Emu oil were selected as oil phase. Tween 80 and Span 80 were selected as surfactants.2-propanol and ethanol were selected as co-surfactants. Optimization of co-surfactant was done by taking a series of O/W microemulsions which were formulated by titration method. 32 formulations were formed initially and based on various physical parameters like clarity, Stability, density, viscosity, pH and electrical conductivity, 17 formulations were narrowed down. The particle size study was carried out by zeta analysis and the results proved that the formulations were nano sized. FTIR studies proved that there was not much interaction between the drugs in the formulation. *In-vitro* dissolution studies were performed for all the 17 formulations individually for both the drugs was found. The optimum formulation where sustained release for both the drugs was found to be in the combination of Oleic acid: Tween 80: Water: 2-propanol (1:3:5:9). This formulation was subjected to *ex-vivo* diffusion study and the permeation through the membrane was found.

INTRODUCTION

Guaifenesin (Narasimha *et al.,* 2012) is a white solid powder that centrally acts as a muscle relaxant with expectorant properties. The molecular mass of Guaifenesin is 198.216 g/mol. It is an over the counter drug that is generally administered orally and has a renal metabolism. Guaifenesin has a melting point temperature of 80ºC and boiling point temperature of 215ºC. Guaifenesin can be stored at a temperature around 15ºC to 25ºC. It is freely soluble in water and has a solubility of 50mg/ml theoretically. The IUPAC name of Guaifenesin is 3-[2-methoxyphenoxy] propane-1, 2-diol. Guaifenesin was first synthesized during the 1940's and is used as an expectorant in the symptomatic management of coughs associated with the common cold. Bronchitis, laryngitis, pharyngitis, pertussis, influenza, measles, and coughs are provoked by chronic paranasal sinusitis. The principal benefit of guaifenesin is in the symptomatic treatment of coughs, associated with the ability of the drug that loosens and thins the sputum and bronchial secretions and eases the expectoration. Guaifenesin acts as an expectorant by increasing the volume and reducing the vicous nature of the secretions in bronchi and trachea.

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Phenylephrine (Gutierrez,2007) is a solid white powder that is generally prescribed for congestion problems. The molecular mass of Phenylephrine is 167.205 g/mol. It is an over the counter drug that is generally administered through Oral, intranasal, ophthalmic, intravenous and intramuscular routes which has hepatic metabolism. Phenylephrine possesses a melting point of 140ºC to 145ºC. The IUPAC name of Phenylephrine is 3-[-1-hydroxy-2-[methylamino] ethyl] phenol. Phenylephrine, a synthetic, sympathomimetic agent that has an alpha adrenoceptor stimulant activity and also possesses Decongestant, vasoconstrictor and bronchodilator activity. It is often given in the combination with other drugs such as an expectorant. It was approved for the usage by the FDA in 1938. Both these drugs (Phenylephrine and Guaifenesin) are freely soluble in water. The pK_a values of these drugs are found to be 14.24 and 15.56 respectively and half life of 2.1 hours and 1 hour respectively. The water solubility of these drugs is found to be 2.20e + 01 g/L and 1.49e + 01g/L. But there arise a question why to go for micro emulsion formulation if the drugs are freely soluble in water. Since the permeability and bioavailability of these drugs are too low, we go for microemulsion formulation to increase the permeability and bioavailability. Microemulsions (Talegaonkar *et al.,* 2008) are optically isotropic, transparent or translucent, low-viscous, singlephasic and

thermodynamically stable liquid solutions. Microemulsions are often termed as critical solutions as they reflect frequently, optical fluctuation and their capacity to solubilize. Microemulsions are bi-continuous systems that are essentially contains water and oil, separated by surfactant and co-surfactant. Microemulsions provide ultralow interfacial tensions. With the use of a single surfactant, it is difficult to achieve the required interfacial area hence a co-surfactant is needed. Microemulsions are generally limited to dermal and peroral application because of their high surfactant concentration. They exist in narrow regions of phase diagrams; therefore they are very restricted in tolerance to quantitative microemulsion changes. Due to the presence of larger interfacial areas microemulsions show much greater solubilizing capacities for both hydrophilic and lipophilic drugs than micellar solutions. Microemulsions are generally limited to dermal and peroral application because of their high surfactant concentration. They exist in narrow regions of phase diagrams; therefore they are very restricted in tolerance to quantitative microemulsion changes.

MATERIALS AND METHODS

Materials

All the chemicals and reagents obtained and used are of analytical grade. Guaifenesin and Phenylephrine were obtained as a gift sample from Gluchem, Hyderabad. Castor Oil was obtained from Chemspure Pvt Ltd., Chennai. Oleic acid, Tween 80, Span 80, and 2-Propanol were obtained from Loba Chemie Pvt Ltd., Mumbai. Ethanol was obtained from Jiangsu Huaxi International Trade Co. Ltd., China. Glycerol was obtained from Merck Ltd., Mumbai. Emu oil was obtained from a local emu farms in southern region of Tamilnadu.

Methods

Optimization of co-surfactant- Preparation of Blank formulation

The O/W microemulsion formulations were prepared by phase titration method (Henri *et al.,* 1988). Oil, surfactant and water ratios were taken as constant (1:1:5 and 1:3:5 respectively) and co-surfactant concentration was optimized by adding it drop by drop to the mixture on a magnetic stirrer. The endpoint of the titration (i.e) the formation of microemulsion is found by phase transition from a white coloured mixture to a transparent mixture. Initially 32 formulations were formed and the formulations are tabulated below.

Table. 1: Components of the initially formed 32 formulations.

S.no	Microemulsion code	Oil: surfactant (ml)	Water (ml)	Co-surfactant (ml)
1	CTI1	1:1	5	20
2	CTI2	1:3	5	13
3	CSI1	1:1	5	30
4	CSI2	1:3	5	30
5	OTI1	1:1	5	12
6	OTI2	1:3	5	9
7	OSI1	1:1	5	20
8	OSI2	1:3	5	28
9	ETI1	1:1	5	70
10	ETI2	1:3	5	50
11	ESI1	1:1	5	40
12	ESI2	1:3	5	65
13	COETI1	1:1	5	30
14	COETI2	1:3	5	30
15	COESI1	1:1	5	40
16	COESI2	1:3	5	45
17	CTEt1	1:1	5	30
18	CTEt2	1:3	5	23
19	CSEt1	1:1	5	50
20	CSEt2	1:3	5	70
21	OTEt1	1:1	5	10
22	OTEt2	1:3	5	8
23	OSEt1	1:1	5	40
24	OSEt2	1:3	5	65
25	ETEt1	1:1	5	85
26	ETEt2	1:3	5	80
27	ESEt1	1:1	5	50
28	ESEt2	1:3	5	80
29	COETEt1	1:1	5	60
30	COETEt2	1:3	5	65
31	COESEt1	1:1	5	70
32	COESEt2	1:3	5	80

Where, (C)- Castor oil, (O)-Oleic Acid, (E)-Emu oil, (T)- Tween 80, (S)- Span 80, (I)- 2-Propanol, (Et)- Ethanol. Numbers 1 and 2 denote the number of formulation based on the ratio. (1)- 1:1 ratio of oil and surfactant, (2)- 1:3 ratio of oil and surfactant.So if the microemulsion code is COETI, then it denotes that the microemulsion contains castor oil, oleic acid, Emu oil, Tween 80 and 2-Propanol.

Preparation of drug loaded formulations

The drug loaded microemulsion formulations were prepared by incorporating the drugs [Phenylephrine and Guaifenesin] in the previously prepared blank formulations. The drug content was then calculated by performing the assay of both the drugs spectrometrically at 213 nm [Phenylephrine] and 273 nm [Guaifenesin].

Evaluation Methods

Physical Parameters

Visual Observation

Visual observation (Patel *et.al*, 2012) of the prepared formulations was analysed. Parameters such as transparency, phase separation are included and the formulations which have better clarity and with no phase separation were confirmed for selection as clarity of the formulation is the initial priority of the microemulsion.

pH

The pH of the prepared 32 microemulsion formulations was determined by using pH meter. The pH was determined by bringing the electrode in contact with the formulations allowing it to equilibrate for a minute. Initially the pH meter was calibrated with suitable calibration solution of pH 4.9 and 7.9 by water. The formulations with pH ranging between 4.5 and 7.5 were confirmed for selection as this range was neither too acidic nor too basic.

Density

The density of the prepared O/W microemulsion formulations was determined using a typical Picnometer. The empty weight of the picnometer is noted. Water is taken up to the

neck of the picnometer and the weight is determined by using electronic balance. Now the difference between the total weight and empty picnometer weight would give the weight of water. Then, the volume of the water that was filled up to the neck was noted which is the volume of the picnometer. The density of water is then calculated.

Then, the prepared microemulsion formulations are taken in the picnometer and the weight is calculated. As the volume is known, the density of the formulations was calculated by the formula,

$$\text{Density[g/mL]} = \frac{\text{Weight[g]}}{\text{Volume[mL]}}$$

Viscosity

The viscosity (Patel *et al.,* 2012) of the microemulsion formulations was determined by Brookfield Viscometer using spindle no.18.

The viscosity of the microemulsion formulations was determined at various 10, 20, 50, 100, 150, 200 rpm operating at 37ºC. Lesser the viscosity, better the administration of the formulation, since less viscous formulations have a better flow property than the high viscous formulations. Hence, less viscous formulations were confirmed for selection.

Electrical Conductivity

The electrical conductivity (Patel *et al.,* 2012) of the formulations was determined by a conductivity meter. Initially, the conductivity meter is calibrated with distilled water and then, the conductivity is obtained by bringing the electrode in contact with the formulations. The electric conductivity was calculated in microSiemens [µS].

Particle size analysis

The particle size (Gundogdu *et al.,* 2011) or the globule size of selected formulations was analysed using zeta-size analysis.

A graph was plotted for size in nm against % of intensity. The size where there was maximum intensity was observed is the mean globule size of the formulations. Particle size analysis was performed to confirm that the formulations were of nano-size range.

Drug Content

The drug content (Won-Tae Kim *et al.,* 2008) eveluation for the selected formulations was done by dissolving 10 mg of drug to 5 ml of the particular formulation. These drug loaded formulations were subjected to assay by analysing it in UV spectrometer at respective λmax [213nm for Phenylephrine and 273nm for Guaifenesin]. The percentage drug content is then calculated by the formula,

$$\%\ \text{Drug content} = \frac{\text{Ma}}{\text{Mth}} \text{X } 100$$

Where, Ma = actual drug content in the formulation

Mth= Theoretical drug content in the formulation

Microscopic Evaluation

Microscopic evaluation (Alia A Badawi *et al.,* 209) was performed by taking images of selected formulations. Initially, a drop of the formulation was placed on the slide and cover slip was placed over it. The slide was then mounted on the microscope and microscopic images were taken in various magnification ranges like 5x, 10x, 20x and 40x to understand the exact morphology of the formulations. Light intensity was adjusted to get clear images of the formulations.

Fourier Transform Infrared Spectroscopy [FT-IR]

FT-IR (MacDonald *et al.,* 1986) was performed in order to find out the compatibility between the drugs in the formulation and also the drugs with other excipients. Analysis was done on Guaifenesin, Phenylephrine and the combined drug in the formulation. Guaifenesin and Phenylephrine were analysed by KBr pellet technique in which the sample was dispersed in KBr and compressed into discs by applying a pressure 5 t for 5 min in a hydraulic press. The pellet was placed in the path of infrared rays and the spectrum was recorded. The formulation containing both the drugs was analysed by ATR where the liquid sample is directly placed on the ATR crystal and subjected to IR rays. A beam of infrared light is passed through the ATR crystal in such a way that it reflects at least once off the internal surface in contact with the sample. The sample absorbs energy and the spectrum was recorded. The samples were scanned in the wave number range from 4000 cm^{-1} to 400 cm^{-1}.

***In-vitro* Dissolution studies**

Among the 32 formulations, 17 formulations [F1 to F17] were selected on the basis of transparency, pH, Density, Viscosity and Conductivity and concentration of Co-surfactant and were subjected to *in-vitro* (Liu D *et al.,* 2013) dissolution in order to analyse the release pattern of the selected O/W microemulsion formulations in the dissolution apparatus using a dialysis membrane. Dialysis membrane was tied at one end of an open ended tube of dimensions 10mm diameter and 20 mm height and 1mL of formulation is poured through the other end and made to be in contact with the membrane. This tube setup is placed in the basket and subjected to dissolution with 100mL water being the media where the media is made to be in contact with the membrane. The other dissolution parameters include temperature of 37ºC at 50 rpm. The dissolution process is carried out for 6 hours to check sustained release and the samples taken at regular intervals and replaced with the same quantity of fresh media to maintain the sink condition and the samples were analysed spectrophotometrically at 213 nm and 273 nm for Phenylephrine and Guaifenesin respectively. The percentage drug release was calculated using standard caliberation curve and the graphs were plotted by taking percentage drug release along the Y-axis and time along X-axis to compare release with respect to time. The similar procedure of dissolution was carried out for the evaluation of the percentage of commercially available syrups of Guaifenesin and Phenylephrine. Later, the percentage release of the drug

loaded selected formulation and commercially available syrups were compared.

Ex-vivo Diffusion studies

From the results obtained in the dissolution analysis, one formulation where sustained release was recorded for both the drugs was continued for *ex-vivo* (Sabale *et al.,* 2012) diffusion studies. This study was carried out in Keshary Chein type diffusion cell using distilled water as the diffusion media. The diffusion cell comprised of a donor and a recipient compartment with a capacity of 5mL and 20 mL respectively. Fresh mucous membrane obtained from goat skin was used as the membrane and the formulation was analysed for permeation in a natural membrane. 20 mL of distilled water was filled in the recipient compartment and 1 mL of the individual drug loaded formulation was placed in the donor compartment. The diffusion cell was setup on a magnetic stirrer and maintained at 37ºC. Sample was taken at regular time intervals and was replaced by the same quantity of fresh diffusion media in order to maintain the sink condition. The study was continued for 6 hours and the % drug release was calculated using standard calibration curve and the graphs were plotted by taking %drug release along the Y-axis and time along X-axis to compare release with respect to time.

Kinetic Modelling study of dissolution data

Drug release kinetics (Hixon and Crowel, 1931, Korsemeyer *et al.,* 1983, Peppas *et al.,* 1985) study helps us in understanding the release pattern and mechanism behind them. There are several linear and non- linear kinetic models available which are classified as Zero order, First order, Higuchi model, Korsmeyer Peppas and Hixson Crowell model. To analyse the drug release mechanism of the formulations data obtained were fitted with these models and the best fit was recorded. Each model follow different rule of kinetic analysis module based on which release pattern are calculated.

RESULTS AND DISCUSSIONS

Physical Parameters

Transparency, pH, Density, Viscosity and Conductivity

The transparency, pH, Density, Viscosity and Conductivity of the 32 formulations were determined. Based on these parameters, the formulations are screened and narrowed down to 17 efficient formulations. They are tabulated as follows.

Transparency increased with the increase in the concentration of surfactant. Increase in the surfactant changed the colour of the formulation but not the clarity. Oleic acid was the oil that provided greater transparency at a very less concentration of co-surfactants. Castor oil, Oleic acid and Emu oil had pH of around 5.5, 4.8 and 6 respectively. The low pH value of Oleic acid is due to its acidic nature. Similarly, decrease in the concentration of co-surfactant decreased the pH value. Increase in the surfactant concentration, decreased the conductivity. Since the surfactants contain lipophilic groups, the conductivity would eventually decrease with increase in the surfactant concentration. Density had no extreme variations. Decrease in the concentration of co-surfactants, increased the density. Based on these parameters, 17 formulations were selected for further evaluation.

Table. 2: Physical parameters of 32 O/W microemulsion formulations.

S.No	Microemulsion Code	Appearance	pH	Density [gm/ml]	Viscosity [cp] @200 rpm	Conductivity [µS]
1	CTI1	Transparent	5.9	0.8155	3.44	52
2	CTI2	Transparent	5.78	0.8981	3.54	26
3	CSI1	Transparent	5.8	0.8322	2.85	56
4	CSI2	Transparent	6.24	0.8158	4.08	37
5	OTI1	Transparent	4.8	0.8768	5.4	67
6	OTI2	Transparent	4.89	0.9615	3.16	20
7	OSI1	Transparent	5.6	0.8243	2.47	55
8	OSI2	Not clear. Excess alcohol	5.85	0.8265	3.12	53
9	ETI1	Transparent	5.7	0.8111	2.28	59
10	ETI2	Transparent	6.46	0.8042	3.18	55
11	ESI1	Transparent but unstable, becomes white when undisturbed	6.2	0.8113	1.95	49
12	ESI2	Translusent	6.53	0.8118	2.86	52
13	COETI1	Transparent	5.7	0.9286	2.67	66
14	COETI2	Transparent	6.24	0.8373	4.5	72
15	COESI1	Transparent	6	0.8167	2.37	54
16	COESI2	Transparent	6.15	0.8237	4.8	59
17	CTE1	Transparent	6.16	0.8410	1.82	48
18	CTE2	Transparent	5.88	0.8470	3.93	25
19	CSE1	Transluscent and not clear	6	0.8013	1.86	51
20	CSE2	Translusent and excess alcohol	6.29	0.8249	1.99	58
21	OTE1	Transparent	5.2	0.9298	3.5	63
22	OTE2	Transparent	4.98	0.9409	4.2	66
23	OSE1	Translusent	5.5	0.8299	1.81	52
24	OSE2	Not formed, cloudy, phase separation	6.08	0.8307	2.02	79
25	ETE1	Translusent excess alcohol	5.6	0.8333	1.8	54
26	ETE2	Not formed, cloudy, phase separation	6.66	0.8149	2.01	48
27	ESE1	Translusent	6.15	0.8226	1.45	43
28	ESE2	Not formed, cloudy, phase separation	6.53	0.8130	1.81	63
29	COETE1	Translusent	5.52	0.8598	1.56	61
30	COETE2	Translusent	6.42	0.8452	1.81	58
31	COESE1	Translusent	5.82	0.8176	1.9	51
32	COESE2	Translusent	6.48	0.8359	3.23	54

Particle Size Analysis

Zeta-size analyser was employed to determine the globule size and surface charge of three randomly selected formulations. The globule sizes were found to be14.27 nm, 89.54 nm, 91.44 and 28.94 for F1, F2, F3 and F11 respectively. This shows that the optimized formulations were nano-sized and could be rightly termed as nano-formulations. The reports are represented below;

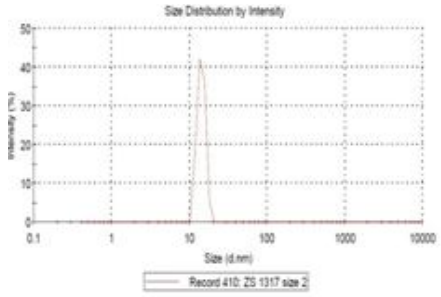

Fig. 1: Zeta-size report of F1.

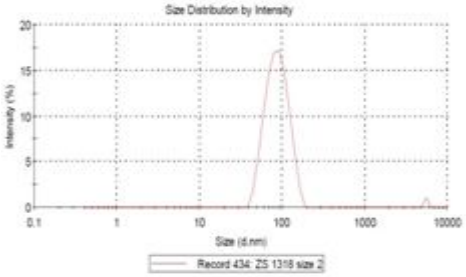

Fig. 2: Zeta-size report of F2.

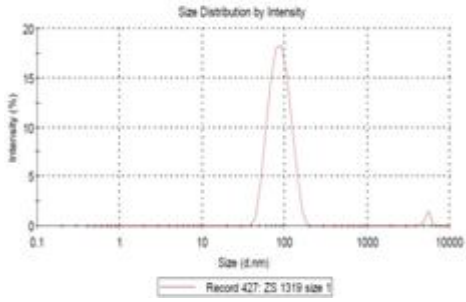

Fig. 3: Zeta-size report of F3.

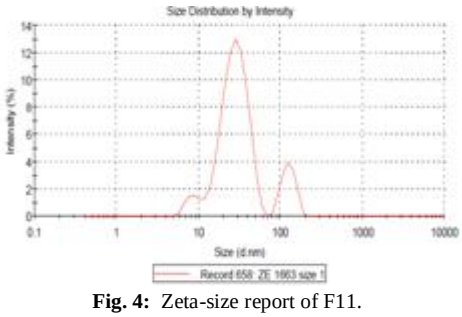

Fig. 4: Zeta-size report of F11.

Microscopic Image

Microscopic images of some selected formulations were taken and are analysed. Oil droplets dispersed in the water medium could be identified from the report. The images are displayed as follows.

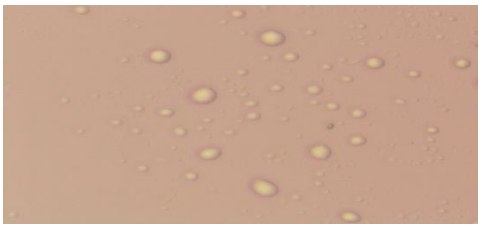

Fig. 4a: 40x magnification of F4.

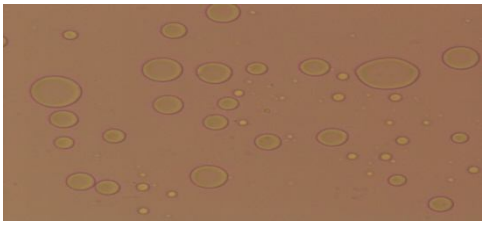

Fig. 4b: 40x magnification of F13.

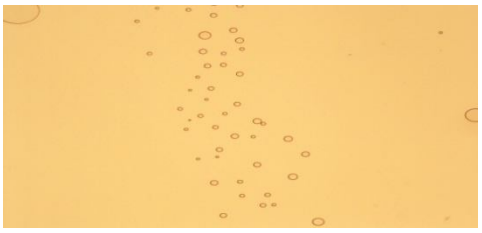

Fig. 4c: 4x magnification of F11.

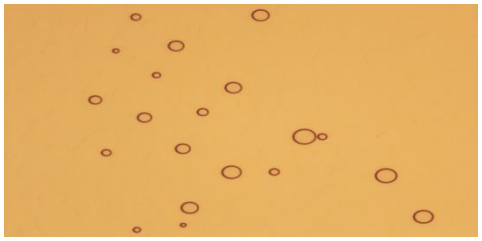

Fig. 4d: 10x magnification of F11.

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR analysis was performed to know whether there was any interaction between the drugs in the combined form. The FT-IR report is represented below.

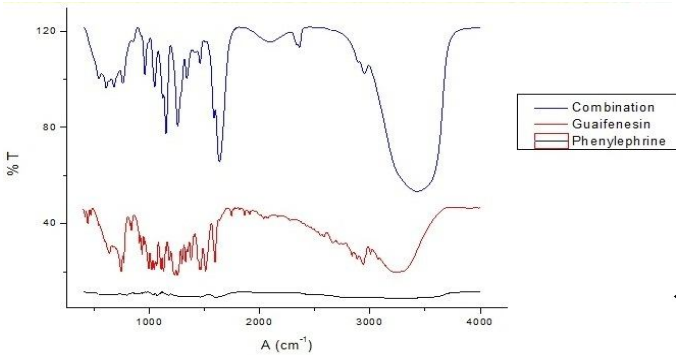

Fig. 5: FT-IR report of Guaifenesin, Phenylephrine and their combined form.

FT-IR spectrum Phenylephrine, Guaifenesin and the combined formulation is shown in the figure 5 [a,b,c]. The IR spectrum in pure Phenylephrine showing peaks at 3267.79 cm^{-1} depicting [OH] alcohol group, 1605.99 cm^{-1} corresponds to amide group[N-H] and 1456.28 cm^{-1} showing the presence of aromatic group [C=C]. Spectrum of pure Guaifenesin showing peaks at 3243.82 cm^{-1} and 1594.29 cm^{-1} corresponds to alcohol group [OH] and amide [N-H], aromatic [C=C] or nitro [N-O] groups respectively.

For the formulation where both the drugs were in combined form, peaks were found at 3431.31 cm^{-1} depicting alcohol group [OH], 1635.74 cm^{-1} corresponding to amide group [N-H] and 1257.76 cm^{-1} depicting an ether group [C-O] or an ester group [C-O]. Comparing these peaks and corresponding groups, there is a shift in peak in the combined formulation [3431.31 cm^{-1}] that shows an alcohol group, and corresponding peaks of the drugs [3267.79 cm^{-1} and 3243.82 cm^{-1}] but showed that they have the same functional group [alcohol group].

Similarly peak of the combined formulation [1635.74 cm^{-1}] and corresponding peaks of pure drugs exhibited that they have the amide group. The other peak in combined form [1257.76 cm^{-1}] and the corresponding peaks in individual drugs depicted that they possess an ester or an ether group. From these interpretations it is unambiguous that there is no interaction between the drugs or any of the excipients in the formulation.

Drug Content

The prepared 32 formulations were screened and narrowed down to 17 formulations on the basis of Clarity, pH, Density, Viscosity, conductivity and co-surfactant concentration. The contents of these 17 formulations are tabulated below. Table3.

Then the drug content was determined in these 17 O/W microemulsion formulations. The content of both Guaifenesin and Phenylephrine was determined spectrometrically at 273 nm and 213 nm respectively. The drug content details are tabulated below Table 4.

Percentage drug content of the selected formulations were found for both the drugs individually. The percentage drug content should be in the range of 90% to 110%. Most of the selected formulations were found to fall in that range except for the formulations that contained Span 80 as the surfactant. That might be due to the presence of the lipophilic surfactant [Span 80] that has a very low HLB value of 1.8.

Table. 3: Composition of finally selected formulations.

S No.	Formulation	Castor oil(ml)	Oleic Acid(ml)	Emu oil (ml)	Tween 80 (ml)	Span 80 (ml)	2-Propanol (ml)	Ethanol (ml)
1	F1	1	---	---	1	---	20	---
2	F2	---	1	---	1	---	12	---
3	F3	---	---	1	1	---	40	---
4	F4	0.333	0.333	0.333	1	---	35	---
5	F5	1	---	---	---	1	25	---
6	F6	---	1	---	---	1	20	---
7	F7	0.333	0.333	0.333	---	1	40	---
8	F8	1	---	---	1	---	---	30
9	F9	---	1	---	1	---	---	10
10	F10	1	---	---	3	---	13	---
11	F11	---	1	---	3	---	9	---
12	F12	---	---	1	3	---	50	---
13	F13	0.333	0.333	0.333	3	---	30	---
14	F14	1	---	---	---	3	30	---
15	F15	---	1	---	---	3	28	---
16	F16	1	---	---	3	---	---	23
17	F17	---	1	---	3	---	---	8

Table. 4: Drug content for the formulations.

S.No	Formulation	Drug content (mg/mL)	
		Guaifenesin	Phenylephrine
1	F1	96.925	96.77
2	F2	102.285	109.4
3	F3	105.895	109.4
4	F4	96.375	107.1
5	F5	102.94	101.1
6	F6	112.8	104.2
7	F7	99.67	103.8
8	F8	84.295	88.21
9	F9	92.895	108.3
10	F10	103.79	98.5
11	F11	109.905	110
12	F12	96.68	93.51
13	F13	104.53	109.5
14	F14	141.21	121.8
15	F15	127.38	114.2
16	F16	109.905	90.9
17	F17	93.185	100.3

***In-vitro* Dissolution studies**

The release percentage at regular intervals were calculated and representaed as follows.

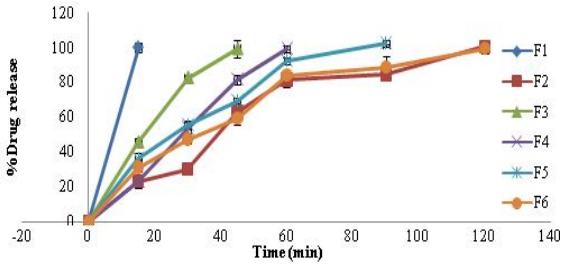

Fig. 5: Percentage release for formulations F1 to F6 (Guaifenesin).

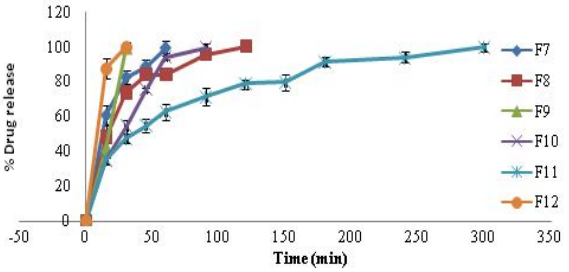

Fig . 6: Percentage release for formulations F7 to F12 (Guaifenesin).

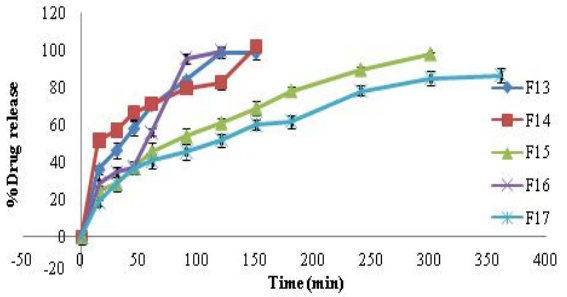

Fig. 7: Percentage release for formulations F13 to F17 (Guaifenesin).

From the release datas of Guaifenesin, the formulations could be used for immediate release of Guaifenesin. Only 3 of the selected formulations show sustained release.

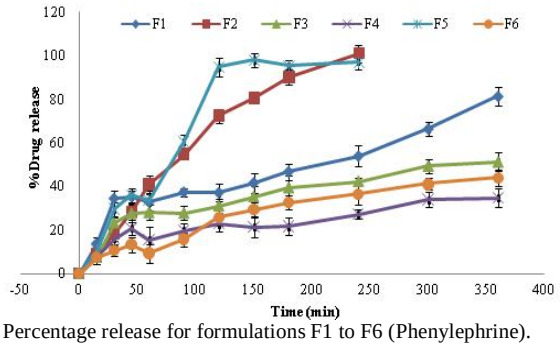

Fig.8: Percentage release for formulations F1 to F6 (Phenylephrine).

From the release data of Guaifenesin and phenylephrine, almost all the formulations could be used for immediate release of Guaifenesin. Only 3 of the selected formulations show sustained release. Release data show that increase in the concentration of the co-surfactant [2-Propanol and Ethanol], the release was quicker, whereas less concentration of these alcohol resulted in sustained release of Guaifenesin. This is because, alcohols have the ability of permeating through membranes easily compared to other compounds. While in Phenylephrine, the release data suggested that all the formulations could be utilized for sustained release.

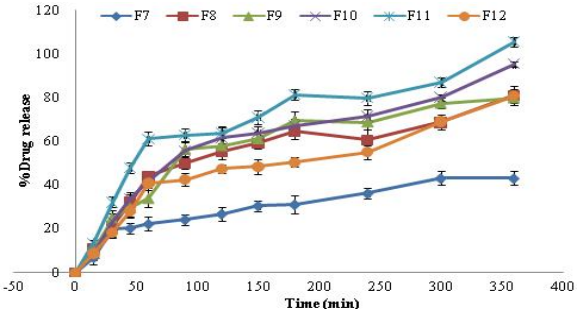

Fig . 9: Percentage release for formulations F7 to F12 (Phenylephrine).

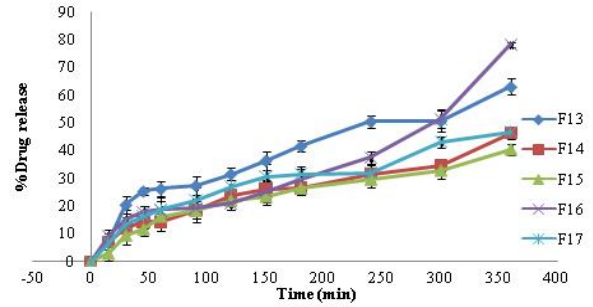

Fig . 10: Percentage release for formulations F13 to F17 (Phenylephrine).

Formulation F11 was chosen as both Guaifenesin and Phenylephrine showed nearly 100% drug release after 6 hours. Rest of the formulations showed a difference in drug release of Guaifenesin and Phenylephrine.

The *in-vitro* dissolution study of the commercially available formulations was also performed and the release was found to be similar to that of the release of the *in-vitro* dissolution evaluation of Guaifenesin and Phenylephrine loaded formulation F11.

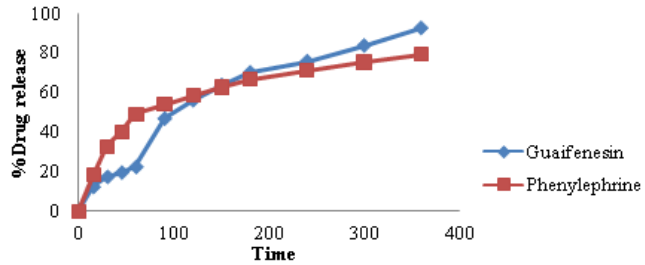

Fig. 11: Percentage release of commercially available Guaifenesin and Phenylephrine

Comparing the formulation F11 that contains Oleic acid, Tween 80, Water and 2-Propanol in the ratio 1:3:5:9, with the commercially available syrup formulation of Guaifenesin and Phenylephrine, F11 has a better release rate after 6 hours than the commercially available syrups. F11 showed a release percentage

of 99.76% and 100.72% after 6 hours. Whereas the commercially available formulations showed a release percentage of 92.62% and 79.26% of Guaifenesin and Phenylephrine after 6 hours. Since the formulation F11 showed a better release after 6 hours than the commercial syrups, F11 was found to be a better formulation for the release of the drugs.

***Ex-vivo* Diffusion Study**.

The *ex-vivo* diffusion study was performed in a Franz-diffusion cell through a mucous membrane of a goat. Water was taken as the medium and samples were taken at regular intervals. The release percentage was calculated individually for both the drugs for the selected formulation F11 as this formulation provided a late release for both the drugs. The release percentage of the drugs is tabulated below.

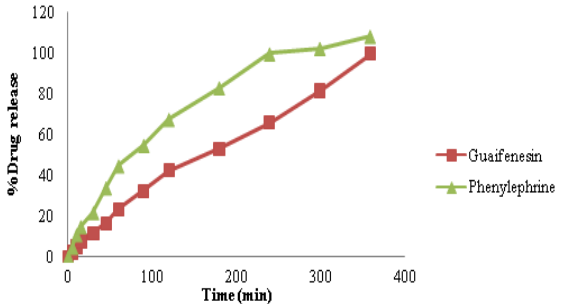

Fig. 12: Percentage release of commercially available Guaifenesin and Phenylephrine.

Comparing the formulation F11 that contains Oleic acid, Tween 80, Water and 2-Propanol in the ratio 1:3:5:9, with the commercially available syrup formulation of Guaifenesin and Phenylephrine, F11 has a better release rate after 6 hours than the commercially available syrups. F11 showed a release percentage of 99.76% and 100.72% after 6 hours. Whereas the commercially available formulations showed a release percentage of 92.62% and 79.26% of Guaifenesin and Phenylephrine after 6 hours. Since the formulation F11 showed a better release after 6 hours than the commercial syrups, F11 was found to be a better formulation for the release of the drugs. From the *ex-vivo* evaluation, the datas showed that the formulation could be effectively used for sustained release of Guaifenesin and Phenylephrine.

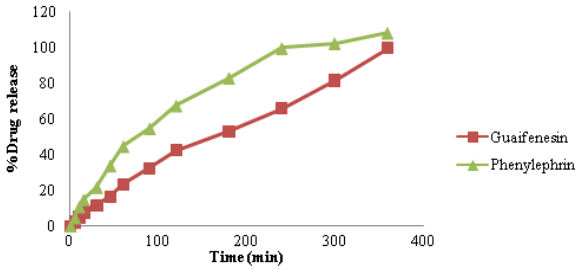

Fig. 13: *Ex-vivo* permeation of Guaifenesin and Phenylephrine.

Release Kinetics

Release kinetics study was performed for both *in-vitro* and *ex-vivo* evaluations. Release study kinetics revealed the type of model that the release follows. The release kinetics datas of *in-vitro* and *ex-vivo* studies are tabulated 12 below.

From the release kinetics datas, most of the formulations followed the release of Hixson-Croxwell model with fikiant mechanism of flow.

The *ex-vivo* diffusion study for the formulation F11 was subjected to release kinetics flow sheet and the reports suggested that both the release of Guaifenesin and Phenylephrine followed the release of Korsmeyer-Peppas model and had a non-fikiant mechanism of flow.

Table. 12: Release Kinetics datas for *in-vitro* release of Guaifenesin.

Formulation	R-sqr values					n value for for Korsmeyer-Peppas model
	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	Hixson-Croxwell model	
F1	0.6182	0.9451	0.9105	0.9476	0.9587	0.685
F2	0.6317	0.9445	0.9221	0.9441	0.9631	0.646
F3	0.7603	0.9715	0.9787	0.9927	0.9915	0.62
F4	0.4306	0.914	0.8948	0.9943	0.9586	0.961
F5	0.7315	0.9722	0.9810	0.9869	0.9870	0.578
F6	0.0184	0.9811	0.9746	0.9754	0.9855	0.525
F7	0.1244	0.8018	0.7771	0.8893	0.7395	0.124
F8	0.2808	0.9904	0.8986	0.9807	0.9688	0.296
F9	0.3543	0.8901	0.8931	1.0000	0.9236	1.242
F10	0.8842	0.9763	0.9723	0.9754	0.9917	0.555
F11	0.1696	0.9429	0.9014	0.9927	0.8852	0.327
F12	0.3993	0.9997	0.9678	1.0000	1.0000	0.190
F13	0.5065	0.982	0.9885	0.9908	0.9760	0.462
F14	0.3384	0.8824	0.8920	0.9827	0.8114	0.296
F15	0.7954	0.9678	0.9970	0.9970	0.9473	0.502
F16	0.7521	0.8918	0.8856	0.9502	0.9231	0.795
F17	0.6177	0.9414	0.9893	0.9918	0.8973	0.465

Table. 13: Release Kinetics datas for *in-vitro* release of Phenylephrine.

Formulation	R-sqr values					n value for for Korsmeyer-Peppas model
	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	Hixson-Croxwell model	
F1	0.6601	0.8829	0.9558	0.9559	0.8338	0.493
F2	0.6882	0.9157	0.9188	0.9210	0.9428	0.536
F3	0.2941	0.4479	0.8783	0.9265	0.4003	0.363
F4	0.8422	0.9246	0.9474	0.9679	0.9030	0.623
F5	0.4204	0.9265	0.9256	0.9469	0.8746	0.407

F6	0.4436	0.6162	0.9132	0.9324	0.5650	0.408
F7	0.7648	0.8779	0.9474	0.9530	0.8477	0.560
F8	0.3980	0.8541	0.8384	0.8507	0.7848	0.425
F9	0.4505	0.8635	0.8454	0.8532	0.8081	0.439
F10	0.4204	0.9265	0.9256	0.9469	0.8746	0.407
F11	0.8136	0.9524	0.9490	0.9647	0.9776	0.403
F12	0.3993	-0.9260	0.9414	0.9559	0.8338	0.493
F13	0.7648	0.8779	0.9474	0.9530	0.8477	0.560
F14	0.7963	0.8758	0.9698	0.9762	0.8533	0.565
F15	0.7951	0.8789	0.9756	0.9825	0.8545	0.566
F16	0.3980	0.8541	0.8384	0.8507	0.7848	0.425
F17	0.4436	0.6162	0.9132	0.9324	0.5650	0.408

Table. 14: Release Kinetics datas for *ex-vivo* release of Guaifenesin and Phenylephrine.

Formulation F11 for	R-sqr values					n value for for Korsmeyer-Peppas model
	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	Hixson-Croxwell model	
Guaifenesin	0.9825	0.9698	0.9130	0.9966	0.823	0.9843
Phenylephrine	0.9448	0.8840	0.9529	0.9960	0.702	0.9029

CONCLUSION

A microemulsion system for the nasal delivery of Guaifenesin and Phenylephrine was prepared using a series of oils, surfactants and co-surfactants.Initially 32 formulations were prepared and tested for their transparency, density, viscosity and conductivity.Based on these parameters, 17 formulations were selected and further continued for solubilising capacity and *in-vitro* dissolution evaluation. From the obtained datas from dissolution evaluation, one formulation which had the capacity of releasing the drug in sustained manner was selected. The formulation was F11 and it had the components Oleic acid, Tween 80, Water and 2-Propanol in the ratio 1:3:5:9 respectively. The *ex-vivo* evaluation was done and the penetration rate of Guaifenesin and Phenylephrine in the formulation was analysed in the Franz Diffusion cell. The result obtained shows a drug Guaifenesin and Phenylephrine drug solubility of 5.198mg/ml and 2.200 mg/ml respectively. The *in vitro* permeation studies showed a 99.76% and 101.72% for Guaifenesin and Phenylephrine respectively. The *ex-vivo* evaluation proved that after 6 hours the release percentage of Guaifenesin and Phenylephrine were 99.61% and 108.103% respectively. Hence F11 may be the most optimum preparation for the nasal delivery of Guaifenesin and Phenylephrine and the developed O/W microemulsion formulation was expected to be potential vehicles for the nasal delivery of the drugs.

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