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Development And Evaluation Of Nanoemulsion Based Darifenacin Hydrobromide Formulation.

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ABSTRACT

The purpose of this research study is to adopt the technology to formulate nanoemulsion that enhances the solubility of drug as reduced drug particle size is considered the most promising strategy to improve drug bioavailability and solubility. Nanoemulsion of Darifenacin hydrobromide was formulated and evaluated for particle size, zeta potential, drug content and drug release. The optimization of nanoemulsion using Central Composite Design was performed. The optimized formula of nanoemulsion was 1:1 Smix ratio and 1:1 Oil to Smix ratio (F1). The optimized batch had optimum particle size (89.4 nm), zeta potential (– 0.4 mV) , drug content (94.12 %) and drug release (88.1 %) The optimized nanoemulsion was compared with available marketed formulation i.e Prolonged release tablets of darifenacin hydrobromide. Compared to the marketed available formulation, the optimized nanoemulsion showed better drug release. The drug release of optimized nanoemulsion formulation was found to be 88.1 % in 60 minutes were as the drug release of the marketed formulation was found to be 88.9 % in 3.5 hrs. The work also includes the development of NE based hydrogel which has shown in vitro drug release of 48.9 % in 5 hours. Also controlled released NE formulation of Darifenacin hydrobromide was developed and evaluated for in vitro drug release which was found to 81.12 % in 17 hours.

Keywords: Darifenacin, Overactive bladder, Drug release.

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INTRODUCTION

Darifenacin hydrobromide is primarily used to treat overactive bladder syndrome. This syndrome is frequently linked with nocturia and urine frequency. The M3 receptor is primarily important for detrusor contraction and, as a result, overactive bladder syndrome. Darifenacin works by inhibiting the M3 muscarinic receptor, which is in charge of bladder muscle spasms. The medication has a low solubility, which results in poor oral absorption [1,2].

Nanoemulsion is transparent, thermodynamically stable, and kinetically stable. It is utilized in the pharmaceutical industry because it improves the bioavailability of lipophilic medications by reducing the particle size of powdered pharmaceuticals and forming nano-sized droplets with a range of (10-100 nm) [3]. A novel drug delivery technique is nanoemulsion. It is one of the innovative drug delivery system techniques for increasing the bioavailability of poorly water-soluble medicines. It consists of an isotropic mixture of oil, surfactant: cosurfactant (Smix), water, and medication [4].

Both high-energy and low-energy approaches can be used to create nanoemulsions[5,6,7]. High-pressure homogenization, high-shear mixing, and ultrasonication are examples of high-energy procedures, whereas spontaneous emulsification and phase inversion methods are examples of low-energy approaches [5-8]. The specific procedure employed is determined on the nanoemulsion's ingredients and intended application.

Nanoemulsions can be utilized to provide drug-loading, drug-solubility, bioavailability, controlled drug release, and targeted drug delivery delivery systems [9]. They are mostly utilized as drug carriers for compounds with low water solubility made up of safe grade excipients [10].

MATERIALS AND METHODS

Materials

Darifenacin hydrobromide, Tween 80, Polyethylene glycol 400. Hariol 538, Mayasol and MCT oil were received as gift samples from Subhash Chemical Industries Pvt Ltd, MIDC Bhosari, Pune-411026, India. Refined Sunflower oil BP, Soyabean oil USP, Sunflower oil USP, Glycerol monocaprylocaprate were received as gift samples from AAK INDIA private limited, Thane(W) – 400607, India.

Method

High-pressure homogenization and ultrasonication.

Experimental work

Preformulation studies:

Characterization of drug

The pure drug sample is evaluated for its colour, odour and its appearance.

Melting point determination.

The melting point of pure drug Darifenacin was determined by melting point apparatus using capillary method.

Calibration of drug by UV spectroscopy [11]

Calibration curve of Darifenacin in 0.1M HCl

Preparation of standard stock solution

Accurately weighed 5 mg of Darifenacin hydrobromide was transferred into the calibrated volumetric flask and dissolved in 5 ml 0.01M HCI Solution to achieve a stock solution of 1000 ug/ml (Stock-

1). Stock- I solution was suitably diluted with 0.01 M HCI to achieve a solution of 100 µg/ml (Stock-II). Stock-II was suitably diluted with 0.01M HCI to achieve a solution of 30 µg/ml (Stock-III).

Preparation of calibration curve

A calibration curve was prepared by diluting the stock II solution to achieve the five different calibration standards representing 10,20,30,40,50 ug/ml strength. The absorbance of each calibration standard was measured at pre identified Λmax 284 nm using fixed wavelength measurement mode. The calibration curve representing concentration vs absorbance was plotted.

Determination of saturation solubility of drug in different oils: [12]

The solubility of darifenacin in various oils, surfactant and co surfactant was determined employing shake flask method and drug content was analyzed using UV-visible spectrophotometer at 284 nm. The solubility of darifenacin in various oils, surfactants and co surfactants were determined by dissolving an excess amount of drugs in 5ml of each selected individual oils, surfactants and cosurfactants contained in stoppered vials separately. The liquids were mixed using a vortex mixer and vials were further shaken using orbital shaker at 37C for 72 hours to reach equilibrium. The samples were determined visually.

FTIR Spectroscopy

IR spectrum of Darifenacin was determined using FTIR spectrophotometer. Baseline correction was done using dried potassium bromide 10 mg of the drug and 50 mg of KBr were alien in a and triturated which were initially dried A small amount of triturated sample was taken and kept in to the sample holder and scanned from 4000cm to 650cm in FTIR spectrophotometer. Then it is matched with official spectra.

Preparation of trial batches of Darifenacin hydrobromide nanoemulsion [12]

Preparation of nanoemulsion by high-pressure homogenization and ultrasonication

Drug and oil were gently stirred and mixed in orbital shaker. Calculated amounts of surfactant (Tween 80) and co surfactant (PEG 400) quantities were placed in vial and gently mixed and volume was made up by distilled water. The mixture was homogenized and probe sonicated . The prepared formulation was evaluated for its particle size, zeta potential, drug content, drug release.

Optimization of nanoemulsion by uing Central Composite Design (CCD) :

Table 1: Composition of different batches of Darifenacin hydrobromide nanoemulsion using CCD

Sr No.	Formulation Batches	Factor 1 (Smix:Oil ratio) ml	Factor 2 (Smix ratio) ml
1.	F1	1	1
2.	F2	1.5	2.20
3.	F3	2	1
4.	F4	1.5	1.5
5.	F5	1	2
6.	F6	1.5	1.5
7.	F7	2	2
8.	F8	1.5	1.5
9.	F9	0.79	1.5
10.	F10	1.5	1.5
11.	F11	2.20	1.5
12.	F12	1.5	1.5
13.	F13	1.5	0.79

The experiments were designed using Design-Expert software Version 121 9

A total of 13 experiments were carried out to study the formulation factors on (Smix ratio), X2 (Oil to Smix ratio) and responses YI (Globule size), Y2 (Zeta potential), Y3 (Drug content), Y4 (Drug release).

Comparison of optimized nanoemulsion with available marketed formulation

As in the market, no immediate release liquid formulation was available, so the prepared formulation was compared with the available Darifenacin hydrobromide prolonged release tablets. Dissolution studies was carried out of the marketed prolonged release tablets.

Formulation and evaluation of NE based hydrogel [13]

The drug was dissolved in mayasol. Further surfactant (Tween 80)and co surfactant(PEG 400) were added. Volume was made up by distilled water and the mixture was homogenized and nanoemulsion was prepared. Eudragit RL100 was used in the ratio of 4:1 (Eudragit:Drug), It was added to the formulation. And further the formulation was incorporated with Carbopol 940(2%) gel. The formulation was evaluated for drug release studies.

Formulation and evaluation of controlled release NE formulation [14]

100 mg of darifenacin was dispersed in 20 ml of oil containing Tween 80, under continuous stirring, further PVA is added and stirring is carried out at 2000 rpm for 5 min at room temperature. The formulation is evaluated for PH, viscosity, particle size, zeta potential, polydispersity index, drug content and drug release.

The in vitro drug release study of this formulation was compared with available marketed controlled release formulation.

Stability Studies of the optimized nanoemulsion formulation

Stability studies of the optimized nanoemulsion was carried out for 90 days. The stability of the optimized formulation was evaluated for its appearance, color, pH and viscosity.

RESULT AND DISCUSSION

Preformulation studies

Organoleptic properties

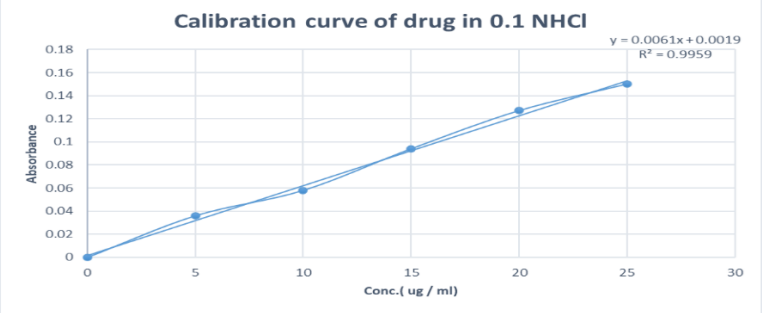
The drug was white solid powder with characteristic odor.The organoleptic properties of pure drug was evaluated and confirmed with the literature.

Melting point determination

The melting point of drug observed was 229 +/- 0.552. The reported melting point is228-230 ^{0}C.

Calibration curve of drug by UV spectroscopy

Figure 1: Calibration curve of darifenacin hydrobromide in 0.1 N HCl.



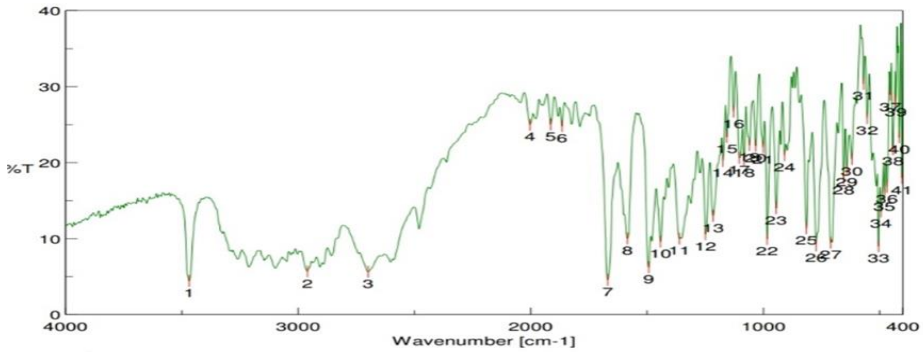
The analytical method (UV) was developed and validated by using 0.1 N HCl as a medium. The linear equation was found to be y=0.0061x+0.0019 and R^2 was found to be 0.9959

Determination of saturation solubility of drug in different oils

The saturation solubility was carried out in peanut oil, Hariol, MCT oils, GMC, Sunflower oil, Soyabean oil, Refined soyabean oil and mayasol. The maximum solubility of drug was observed in mayasol in comparison with the other selected oils.

FTIR studies

Figure 2: FTIR Spectrum of Darifenacin hydrobromide.



The observed functional group were N-H stretch, C=O stretch, C=C aromatic stretch, ether stretch, C-H aromatic stretch. The FTIR spectra of the pure drug was found to be complied with the standard FTIR spectra of the drug.

Evaluation of trial batches of Darifenacin hydrobromide nanoemulsion

Table 2: Results of trial batches of Darifenacin hydrobromide nanoemulsion

Sr no.	Trial Batch	Particle size(nm)	Zeta Potential (mv)	Polydispersity Index	Drug content(%)
1.	Batch 1	1015.6	-37.5	0.551	90.12
2.	Batch 2	658	-1.6	0.685	92.08
3.	Batch 3	556.1	-4.1	0.469	92.88
4.	Batch 4	247.2	-2.4	0.397	91.23
5.	Batch 5	89.6	-0.5	0.552	95.81

All the trial batches were evaluated for particle size, zeta potential, drug content and drug release. Batch 4 has shown good results in comparison with Batch 1, Batch 2, Batch 3.

In Batch 5 the oil phase was changed, here mayasol was used as an oil phase. This batch showed more good results compared to batch 4.

Optimization of nanoemulsion by uing Central Composite Design (CCD) :

The composition of nanoemulsion finalized as per batch 5 was further optimized using central composite design.

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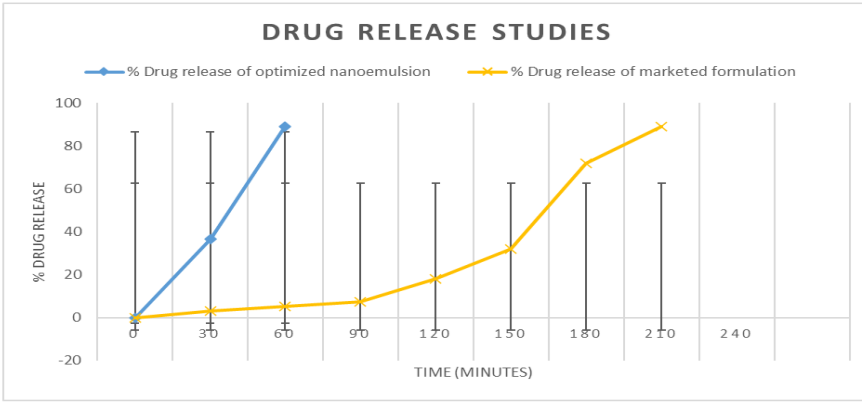
Table 3: Response of Central Composite Design formulation of darifenacin nanoemulsion

Sr No.	Formulation Batches	Particle size (nm)	Zeta potential (mV)	Drug content(%)	Drug release(%)
1.	F1	89.4	-0.1	93.1	88.9
2.	F2	55	-0.35	93.8	95.6
3.	F3	48	-0.1	92	98.9
4.	F4	89.5	-0.3	97.8	90.1
5.	F5	47.7	-0.3	94.76	98.9
6.	F6	89.5	-0.35	97.8	90.01
7.	F7	64.4	-0.5	97	91.3
8.	F8	89.5	-0.3	97.8	90.01
9.	F9	50	-0.26	96	95
10.	F10	89.5	-0.3	97.8	90.01
11.	F11	65	-0.35	95.8	94.6
12.	F12	89.5	-0.3	97.8	90.01
13.	F13	65	-0.2	94	97

The optimized formula of nanoemulsion was 1:1 Smix ratio and 1:1 Oil to Smix ratio (F1). The optimized batch had optimum particle size 89.4 nm, zeta potential – 0.4 mV , drug content 94.12 % and drug release 88.1 %

Comparison of optimized nanoemulsion with available marketed formulation.

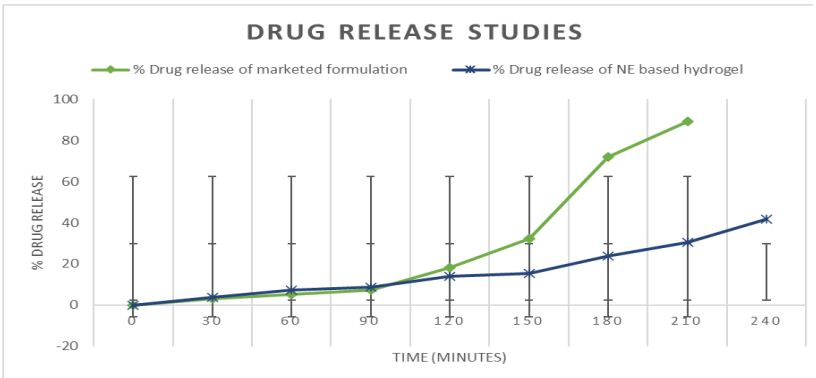
Figure 3: Comparison of optimized nanoemulsion with available marketed formulation.



The in vitro drug release of optimized nanoemulsion formulation was found to be 88.1 % in 60 minutes were as the drug release of the marketed formulation was found to be 88.9 % in 3.5 hrs.

Formulation and evaluation of NE based hydrogel

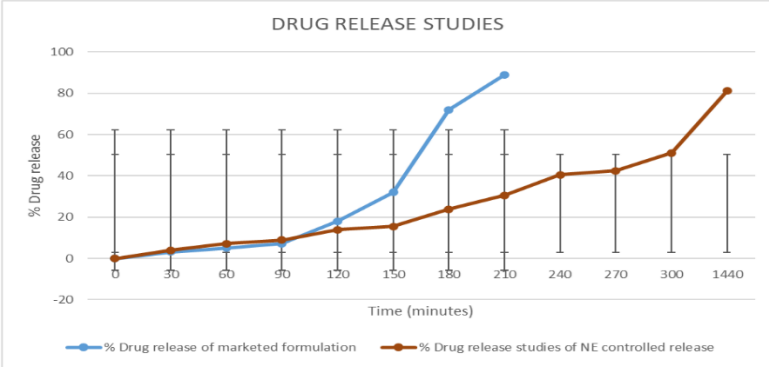
Figure 4: Comparison of NE based hyrogel with available marketed formulation.



In the present experiment, the optimized NE (F1) was converted into a hydrogel and it was observed that the drug release was found to be 48.9 % in 5 hours were as the drug release of the marketed formulation was found to be 88.9 % in 3.5 hrs.

Formulation and evaluation of controlled release NE formulation

Figure 5: Comparison of NE controlled release formulation with available marketed formulation



The in vitro controlled released NE formulation of Darifenacin hydrobromide showed drug release of 81.12 % in 17 hours were as the drug release of the marketed formulation was found to be 88.9 % in 3.5 hrs.

Stability Studies of the optimized nanoemulsion formulation

Table 4: Stability Studies of the optimized nanoemulsion formulation

Sr No.	Parameter (n=3, Avg =/- SD)	0 days	30 days	60 days	30 days
1.	Appearance	Liquid	Liquid	Liquid	Liquid
2.	Color	Transparent	Transparent	Transparent	Transparent
3.	pH	6.8	6.8	6.7	6.9
4.	Viscosity	1656 +/- 4.72 at 100 rpm	1691 +/- 4.72 at 100 rpm	1662 +/- 4.72 at 100 rpm	1666 +/- 4.72 at 100 rpm

As per ICH stability studies, it was found that the optimized NE formulation was stable for selected formula at accelerated conditions.

CONCLUSION

The present research work is a novel approach of development of NE based liquid dosage form of darifenacin. The work includes the formulation development, optimization and evaluation of NE of darifenacin. The in vitro drug release of optimized nanoemulsion formulation was found to be 88.1 % in 60 minutes were as the drug release of the marketed formulation was found to be 88.9 % in 3.5 hrs. The work includes the development of NE based hydrogel which has shown in vitro drug release of 48.9 % in 5 hours. Also controlled released formulation of Darifenacin hydrobromide was developed and evaluated for in vitro drug release which was found to 81.12 % in 17 hours. This work showed potential of nanoemulsion form of the Darifenacin which promises the more patient compliance and effective dosage of darifenacin.

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