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DEVELOPMENT AND VALIDATION OF TITRIMETRIC METHOD FOR ESTIMATING POTENCY OF DRUG 5-BENZYL 1, 2, 3, 4- TETRAHYDRO-2-METHYL ϒ CARBOLINE NAPHTHALENE 1, 5 DISULPHONATE

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ABSTRACT
The drug development is a long process and the nonaqueous titrations play vital role in drug development via monitoring the synthesis of drug intermediates and finally the drug itself. Mebhydrolin Napadisylate is an H_1-receptor blocking antihistamine drug which is white powder and odourless in physical state. It is used in Hay fever, Rhinitis, Urticaria, Angioedema, Eczema and other allergic conditions. Mebhydrolin forms a salt with 1, 5 Naphthalene disulphonic acid (Napadisylic acid) to give rise to Mebhydrolin Napadisylate. The potency of drug is monitored by performing nonaqueous titration against perchloric acid using crystal violet as indicator. The method gives reliable results with least labour. The method is cost effective since high instrumentation is no more required in this method. The accuracy of the method was evaluated in total fifteen replicates as intraday and interday analysis taking three different concentrations within range of Mebhydrolin Napadisylate. The ruggedness and recovery study was also carried out to ascertain the reliability of the method.

KEYWORDS: Nonaqueous Titration, Mebhydrolin Napadisylate, Perchloric acid.

INTRODUCTION
Drug development is a lengthy process which involves lot of hard work and patience. There are numerous instrumental and non-instrumental techniques widely used in drug development such as HPLC[5], Mass Spectrometry[8], Ultra-performance liquid chromatography[4] and Visible spectrophotometry[3] but these techniques are costly and involve high instrumentation. The titrimetric methods[2,7,12] are easy operating, cheaper in cost and accurate. The non-aqueous titrations are quite helpful in determining the drug status by measuring the potency of drug. El-Kommos et al.[1] and Mahgoub H et al.[11] also worked out suitable procedures for analysis of antihistamine drugs. The present paper deals with the determination of potency of drug Mebhydrolin Napadisylate which is a 5-benzyl 1,2,3,4- tetrahydro-2-methylϒcarbolinenaphthalene 1, 5 disulphonate by non-aqueous titration using crystal violet as indicator. The present titrimetric method is of high importance where HPLC is not available. Mebhydroline forms a salt with 1, 5 Naphthaline disulphonic acid (Napadisylic acid) forming the drug molecule Mebhydrolin Napadisylate. The present titrimetric method gives reliable results with least labour. The method was developed by performing drug assay against acetous perchloric acid as a titrant in nonaqueous medium and acetous crystal violet as an external indicator. The validation of method was also carried out by evaluating various parameters. During titrations blank was also run and final titer values were subtracted from blank to get the actual volume of perchloric acid consumed in titration. The method shows good accuracy and precision with least labour.

MATERIAL AND METHODS
The acetous per-chloric acid **(**$HClO_4$) of 0.1 M strength was prepared in glacial acetic acid and standardized with potassium hydrogen phthalate. The Crystal violet indicator of 0.1% w/v was also prepared in glacial acetic acid. The drug molecule of Mebhydroline Napadisylate was used as an active drug molecule without excipients. All chemicals of laboratory grade are used in the experiment.

SAMPLE PREPARATION
Sample solution of Mebhydrolin Napadisylate was prepared in glacial acetic acid by dissolving accurately weighed 100 to 450 mg of drug in a separator and added 25 ml of 1.0 N NaOH and 50 ml $CHCl_3$. Shaking was done for five minutes and allowed the two layers to separate. Now we took the lower $CHCl_3$ layer into the another separator by passing through anhydrous Na_2SO_4. The upper aqueous layer was further extracted with three 50 ml portions of $CHCl_3$. Water wash was given to get

rid of alkali and passed the extract through Na_2SO_4 pledged on cotton. Ensuring that there should not be any appearance of red color with phenolphthalein indicator. Now all the $CHCl_3$ extracts were collected into 500 ml round bottom flask and $CHCl_3$ content was removed on rotary evaporator to get the dry mass.

ASSAY OF DRUG

The Assay of drug was carried out by dissolving the dry mass as obtained above in 25 ml of glacial acetic acid. Four drops of crystal violet (0.1% w/v) indicator were added into 250 ml dry titrating flask and titrated against standardized 0.1 M acetous perchloric acid. The titration was continued till the generation of green end point from initial violet color. The blank titration was also performed and necessary corrections were made in the calculations. Various sets of active drug molecules ranging from 100 mg to 450 mg were undertaken and titrated in the same fashion.

The amount of Mebhydroline Napadisylate in the prepared aliquot was calculated as:

Amount of Mebhydroline Napadisylate (mg)=V x M x MW/ n

Where V= ml of $HClO_4$ consumed, M= Molarity of $HClO_4$, MW= molecular Weight of Mebhydroline Napadisylate and n= Number of moles of $HClO_4$ reacting with each molecule of Mebhydroline Napadisylate.

STRUCTURE AND CHEMISTRY

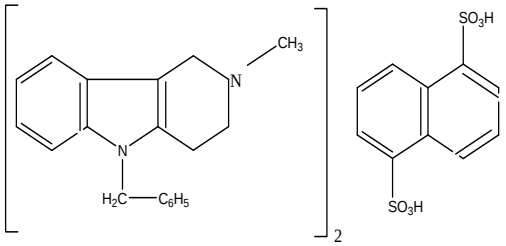

Fig. 1

The potency of drug Mebhydroline Napadisylate was evaluated by nonaqueous titration which is basically a neutralization reaction. In this reaction Mebhydroline Napadisylate act as base and acetous $HClO_4$ acts as strong acid. The amphiprotic property[9] of CH_3COOH makes it ideal solvent for nonaqueous titrations. The onium ion[6] (CH_3COOH^{+2}) is formed when $HClO_4$ is dissolved in CH_3COOH because of the donation of proton by $HClO_4$, the same proton is accepted by CH_3COOH i.e. here CH_3COOH acts as base. The onium ion donates its proton to Mebhydroline Napadisylate. The stoichiometry of the reaction was found to be 1:2 (Mebhydroline Napadisylate: $HClO_4$)

RESULTS AND DISCUSSION

The development of drug was monitored by taking drug from final step and subjecting it to analytical assessment by measuring the drug assay with the help of non-aqueous titrations. Various parameters of the present method were evaluated to validate it as per ICH guideline.[10]

ACCURACY AND PRECISION

The accuracy of the method was evaluated in total fifteen replicates as intraday and interday analysis taking three different concentrations within range of Mebhydroline Napadisylate. The accuracy is reported in terms of percent relative error between the observed amount and the amount taken. Precision is also evaluated as intraday and interday evaluations in terms of % RSD value (Table 1).

RUGGEDNESS

The ruggedness of the method was also performed to further ascertain the degree of reproducibility of the method by four different analysts using three different burettes. The ruggedness was reported in terms of % RSD (Table 2).

RECOVERY STUDY

The recovery studies of the developed method were also undertaken to ascertain the reliability of the method by spiking pure Mebhydroine Napadisylate of 50, 100 and 150 mg in the sample at three different concentration levels (Table 3). The comparison of results is also made with reference method (table 4).

Table-1 (Intra and inter-day accuracy and precision).

Mebhydroline Napadisylate taken (mg)	Intra-day, n=5			Inter-day, n=5		
	[a]Mebhydroline Napadisylate found (mg)	RSD %	RE%	Mebhydroline Napadisylate found (mg	RSD %	RE%
100	99.33	2.0	-0.67	99.34	1.23	-0.66
250	249.69	0.80	-0.12	249.24	0.49	-0.30
450	450.15	0.54	0.03	450.60	0.27	0.13
a:Mean value of n determinations, RSD: Relative standard deviation, Percent relative error: Amount found-Amount taken x100/ Amount taken						

Table-2 (Ruggedness in terms of precision).

Mebhydroline Napadisylate analysed (mg	Inter-analyst, RSD% (n=4)	Inter-burettes, RSD% (n=4)
100	1.05	1.11
250	0.92	1.04
450	0.82	1.01

Table-3 (Recovery study using standard addition method).

Mebhydroline Napadisylate analysed (mg)	Mebhydroline Napadisylate added (mg)	Total Mebhydroline Napadisylate found (mg)	Pure Mebhydroline Napadisylate recovered (Percent ± SD
250	50	299.05	98.10 ± 1.29
250	100	349.77	99.77 ± 1.03
250	150	398.99	99.33 ± 1.01

Table-4 (Assay comparison results between Reference & Proposed method).

Mebhydroline Napadisylate analysed (mg)	Reference Method (Assay Percent ± SD)	Proposed Method (Assay Percent ± SD)
100	99.23 ± 1.01	99.33 ± 1.03
250	99.70 ± 1.03	99.88 ± 1.04
450	100.13 ± 1.06	100.03 ± 1.10

CONCLUSION

The quantification of Mebhydroline Napadisylate drug from proposed non-aqueous titrimetric method is simple, non-complicated and precise showing good accuracy. The main advantage of the present titrimetric method is that it is cost effective and does not require high instrumentation which is quite costly.

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