WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 3, 12-22 Research Article ISSN 2278 – 4357

DIOCTAHEDRAL SMECTITE API' ANALYTICAL METHOD DEVELOPMENT AND VALIDATION ON TITRIMETRIC METHOD FOR THE QUANTITATIVE AND QUALITATIVE DETERMINATION OF IN ORAL DOSAGE FORM.

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Article Received on
25 Nov. 2018,

Revised on 15 Dec. 2018,
Accepted on 04 Jan. 2019,

DOI: 10.20959/wjpps20193-13256

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ABSTRACT

Back Ground[1]: The Dioctahedral Smectite belonging to a Smectite group (derived from the Greek, smectos, which means soap) indicates large chemical inconsistency, consequential in many detailed mineral names (Gwyn 1988). The substance has been studied in aspect way in by X-ray diffraction in the past, but we have worked on it by a titrimetric method cheapest analytical techniques as compare to X-ray diffraction.

Drug Administrative Benefits of Dioctahedral Smectite (DOS)[2]
Dioctahedral Smectite used for the symptom of chronic diarrhea, nausea. Diarrhea and vomiting in children with gastroenteritis diagnosis, assessment and management in youngsters of just five years. ***Dioctahedral Smectite (DOS)[3]:*** Is used for acute and chronic diarrhea, especially in children. Also used in esophageal and colonic disorders and other stomach infections. And also used for severe and long-lasting diarrhea Gastro esophageal reflux in child. Short-tempered bowel disease in adults and other conditions as well.

Structure & Formulation Difference Between Montmorillonite & Dioctahedral Smectite

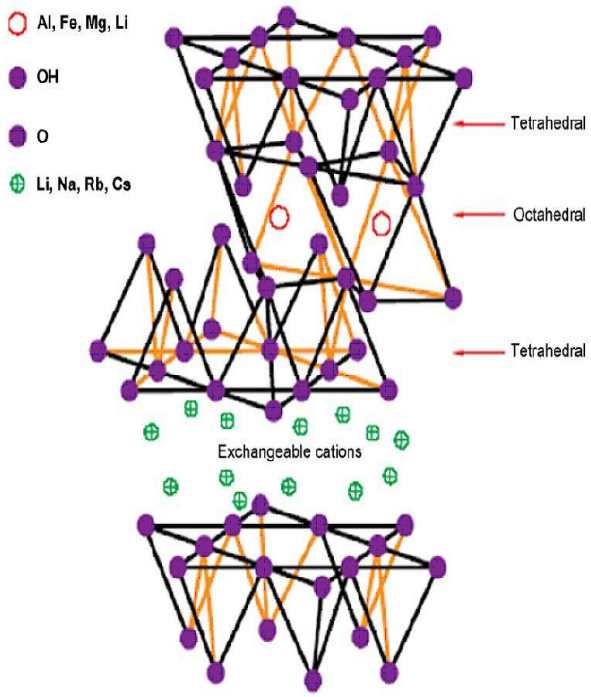
The most common smectite mineral is montmorillonite, which has the following representative chemical formula: $X_{.3}{\cdot}nH_2O\ [(Al_{1.5}Fe^{3+}{}_{.2}Mg_{.3})Si_4O_{10}(OH)_2]^{-.3}$,...(*formula - 01* montmorillonite) smectite with molecular weight: ***360.307 g/mol***. The pre-edge scale of

montmorillonite is similar to ranges normally stated for dioctahedral smectite. Dioctahedral Smectite Molecular Formula.

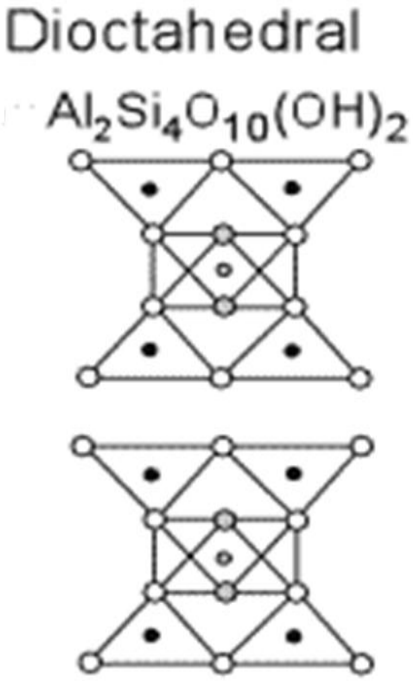
$A_{0.3}D_{2\text{-}3}[T_4O_{10}]Z_2 \cdot nH_2O$[4] ……(formula – 02 for dioctahedral smectite)

Having molecular mass ***282.21/ mole***. There is a divergence, the pre-edge spectrum of hectorite clay is particularly separate, remarks to either variances in the site symmetry or in covalence as well. Formulation of Dioctahedral Smectite: $A_{0.3}D_{2\text{-}3}[T_4O_{10}]Z_2 \cdot nH_2O$ See below structure.[5]

Montmorillonite Smectite Figure -01



Dioctahedral Smectite Figure -02



The API and product contributed by Nexus Pharma Pvt Ltd Pakistan. Dioctahedral Smectite API sourced by Zhejiang Camp-Shinning New Material Co., Ltd a china origin company.

KEYPOINTS: Dioctahedral Smectite API & Finished Dosage Form Qualitative & Quantitative Determination By Titrimetric Mod.

INTRODUCTION

The Dioctahedral Smectite a inorganic mineral compound belong smectite also recognized as ***swelling clay*** is a mixed-up group of clay natural resources. Dioctahedral Smectite to begin with studies on X-ray diffraction techniques. We started working quite a lot of reagents initial phases and finally, we achieve to develop a method by titrimetric analytical

assessment of ***Dioctahedral Smectite*** molecule with, titrate with 0.05M Ethylenediaminetetraacetic acid. (EDTA) using *Eriochrome Black-T as an indicator*, blue color obtained at the end in blank solution, The Concentration Of API (Active Pharmaceutical Ingredient) was accurately weigh 10 mg/mL for 100% solution.

LINEARITY

Assay linearity was demonstrated by preparing five standard solutions within the liable range of ~80%,90%,100%,110% and 120%, each concentration prepared two time from lower to higher 8.0 mg ---- 12 mg /mL. the linear observed on the five individual concentration prepared twice and correlation coefficient (R^2 0.9992) and linear regression Y = 0.0072 x + 0.1588. Respective stated attributes data. Pharmaceutical Ingredient Octahedral Smectite including FPP (Finished Pharmaceutical Product) sample of Nexdrol 3 gram per Sachet (Octahedral Smectite) dosage performed for further verification of product response in sample for accuracy and precision shown in summary report. The method validation reference tackles were in use from ICH guidelines,[6] united states pharmacopeia 'USP' general chapters of method validation[7] & Verification,[8] and the fitness for purpose of analytical methods.[9]

❖ **SUPPLEMENTS**

The analytical procedure definitions alike, Identification, System suitability, Accuracy, Precision, linearity, Range Limit Detection (LOD), Limit of Quantitation (LOQ) Robustness, Reproducibility should be defined in to method validation protocol in details.

1. MATERIALS AND METHOD

1.1 Reagents

i) Ethylenediaminetetraacetic acid. (EDTA).
ii) Eriochrome Black T (Indicator)
iii) Ammonium-Ammonium Chloride Solution
iv) Glass Burette
v) Beakers, Conical Flask, Pipettes
vi) Water, pharmaceutical grade water.

1.2 Instrumentation

''MANUAL TITRATION''

1.3 Analytical Testing Method Procedure

Diluent: Water

Standard & Sample Preparation: ***(Standard preparation for identification only)***

a. Weigh 1000 mg of Dioctahedral Smectite working standard into a 500 mL conical flask. Add 100 mL of distilled water to dissolve, shake well for fifteen minutes on orbital shaker.
b. Add 5 mL ammonia-ammonia chloride buffer, the concentration of standard is approx. 10 mg/mL
c. Add 0.1 mL to 0.3 mL *Eriochrome Black T,* titrate with 0.05 M (EDTA) Ethylenediaminetetraacetic acid.
d. Precede same method for blank determination.

Sample Preparation

a. Weigh and finally powder not less than 10 Sachet. Transfer an accurately weighed portion of the powder equivalent to product sachet filled weight 3000 mg of Dioctahedral Smectite into a 500 mL conical flask.
   Add 100 mL of water dissolve, shake well for fifteen minutes on orbital shaker.
b. add 5 mL ammonia-ammonia chloride buffer.
c. Add 0.3 mL *Eriochrome Black T,* titrate with 0.05 M Ethylenediaminetetraacetic acid (EDTA.
d. Each ml of 0.05 M Ethylenediaminetetraacetic acid (EDTA) against, is equivalent to 14.11 mg of Dioctahedral Smectite.

➢ ***[Note]*** Standard and Sample both point toward pink colour, while blank give the show slightly violet colour before titration. After Titration blank shows end point with light green colour and standard and sample conclusively given green colour. Further see figures 2.1 in identifications.

Calculation for API $= \frac{Vs \times F \times 14.11 \text{ (Concentration mg/ mL)}}{\text{Weight of API (mg/mL)}}$

Calculation for Product

Potency % / Sachet $= \frac{Vs \times F \times 14.11x \text{ Avg Wt}}{Wsp}$

Where,

Vs = Volume of 0.05M Ethylenediaminetetraacetic acid (EDTA) consumed in sample.

F = Is the factor volumetric solution of 0.05M (EDTA)

Avg: Wt = Average Weight of sample (or taken weight of API)

14.11 = Equivalent Factor.

Wsp = Weight of sample taken for Product assay (API Assay)

1.4 *The Validation Characteristics Points*

The method validated task comprises on stated below parameters.

Such as, Identification (by titration) Accuracy, Precision, linearity, Range Limit Detection (LOD), Limit of Quantitation (LOQ).

1.5 *Abbreviations*:

DOS	=	Dioctahedral Smectite
U.S. FDA	=	United States, Food And Drug Administration
USP	=	United State Pharmacopeia
API	=	Active Pharmaceutical Ingredient
FPP	=	Finished Pharmaceutical Product.
HC	=	Health Canada
ICH	=	International Conference on Harmonization
QTY	=	Quantity
VS	=	Versus

2. Attributes are under Analysis by Dioctahedral Smectite.

❖ **Following factors were evaluated**

1. **Identifications.**
2. **Linearity**
3. **Range**
4. **Precision**

4.1 Repeatability

4.2 Intermediate Precision

5. **Accuracy (Spiked Placebo Method)**
6. **Specificity**

2.1 IDENTIFICATION BY TITRATION

Specificity Terms

The identification of API of Octahedral Smectite determined on different analysts at different event to know the exit behavior at stating point and conclusive point as well. Below picture represent before and after titration behavior of Blank, API, and sample constituents at the encoded concentration 10 mg/mL, *(Follow the method part 1.3).*

Appearance

The appearance of standard and sample both indicate pink colour, while blank shows slightly violet colour before titration. Subsequently, after Titration when blank shows end point with green colour, in case of standard and sample end point specify green colour as well.(see figure.2.1).

2.2 Standard Preparation

The linearity graph observed on the five individual concentration prepared twice and find the correlation coefficient (R^2 0.9992) and linear regression Y = 0.0072 x + 0.1588, surrounded by 80%, 90%, 100%, 110% & 120%, concentrations, (8 mg/mL to 12 mg/mL individually) see fig 2.2.1. The detailed concentration results are decisively characterized in Table 2.2.2 for 'Dioctahedral Smectite' see below Linearity Diagram Fig. 2.2.1.

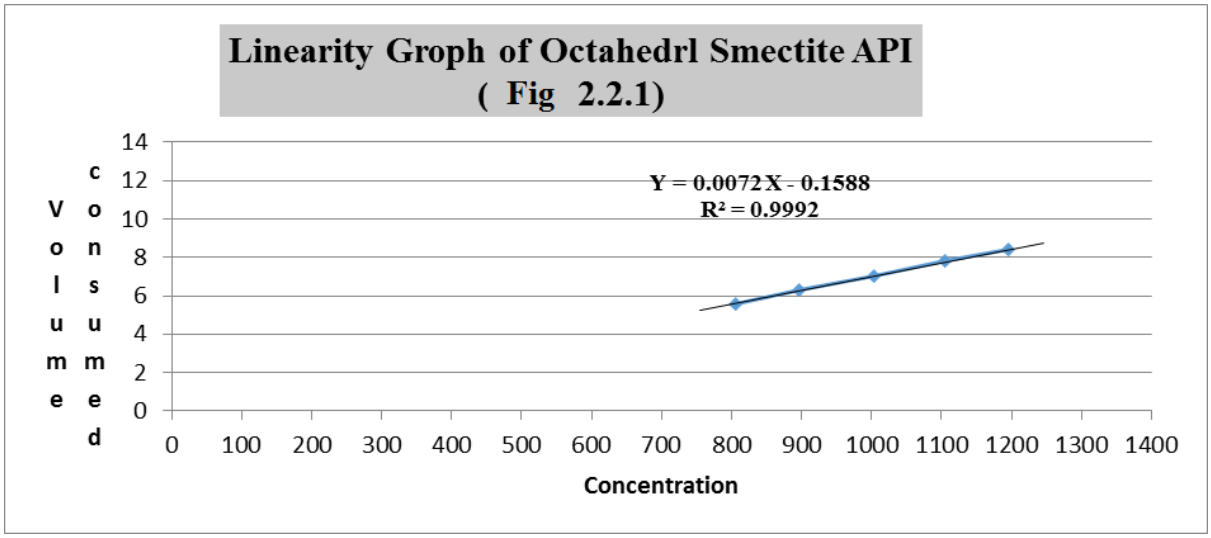


Table 2.2.2 (Dioctahedral Smectite).

Linearity Outcomes of Dioctahedral Smectite API (table 2.2.2)				
Target Level	**API Concentration 10 mg/ mL**	**(Dioctahedral Smectite) Response**	**Volume Average**	**% RSD**
80%	805.5	5.60	5.6	0.00
		5.60		
90%	895.5	6.30	6.3	0.00
		630		
100%	1002.758	7.00	7.0	0.00
		7.00		
110%	1105.50	7.80	7.7	0.00
		7.80		
120%	1195.5	8.40	8.4	0.00
		8.40		
Correlation Coefficient (NMT 1.0%) =0.9992				

2.3 Range

Here five different concentration of sample alike linearity, prepared of 80%, 90%, 100%, 110% & 120%, (8 mg/mL to 12 mg/mL individually). The correlation coefficient (R^2 0.9997) and linear regression Y = 0.002 x + 0.15 are shown in graph fig.2.3.1 while acceptance

criteria and results are represented in table 2.3.2 (***Dioctahedral Smectite)*** finished pharmaceutical product (FPP). See below graph fig 2.3.1 and table 2.3.1

Product Range Diagram Fig. 2.3.1

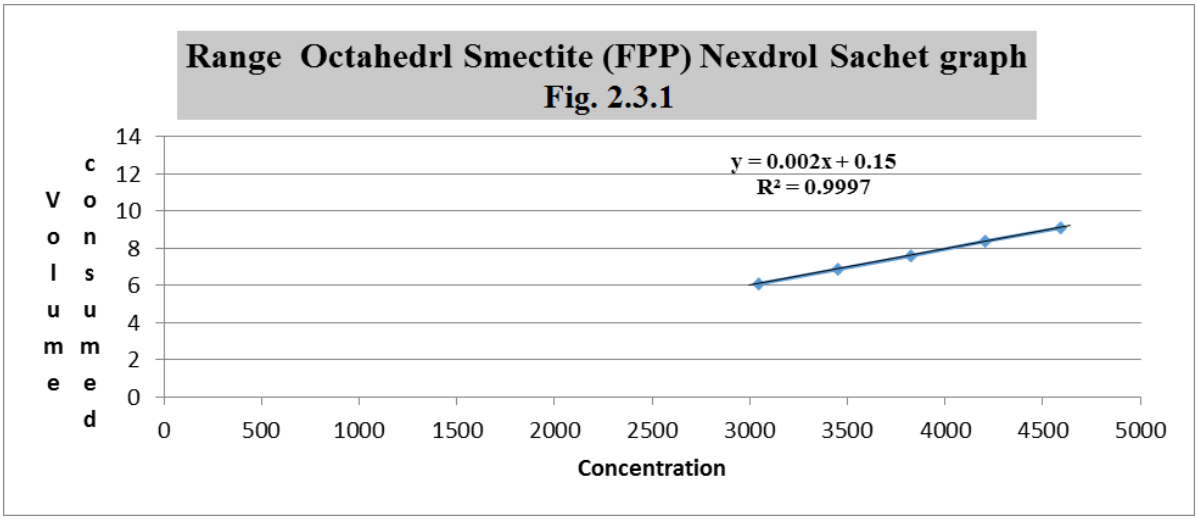


Table 2.3.2.

Range of Dioctahedral Smectite *for Assay Determination. Table (2.3.2)*				
Target Level	**FPP, Concentration 10 mg/ mL**	**(Dioctahedral Smectite) Response**	**Volume Average**	**% RSD**
80%	3045.50	6.1	6.1	0.00
		6.1		
90%	3452.50	6.9	6.9	0.00
		6.9		
100%	3824.20	7.6	7.6	0.00
		7.6		
110%	4205.5	8.4	8.4	0.00
		8.4		
120%	4588.30	9.1	9.1	0.00
		9.1		
Correlation Coefficient (NMT 1.0%) = 0.9997				

2.4 PRECISION

2.4.1 Repeatability

i. The ten samples were prepared of 10mg/mL 100.0% concentration accordingly, by focusing a set object to regulate the exactness of the analytical method over on over reprising yield a conclude with in limit RSD % 0.80% with 100.68% assay results. Further outcomes are offered in below table 2.4.1.

(***Dioctahedral Smectite***) Table 2.4.1.

Sample #	Sample Weight (mg)	Volume consumed *Dioctahedral Smectite*	Theoretical Claim 100%	Obtained Results %
1	10 mg/mL	7.0	100.00%	101.30
2	10 mg/mL	7.0	100.00%	99.74
3	10 mg/mL	7.1	100.00%	101.30
4	10 mg/mL	7.1	100.00%	101.30
5	10 mg/mL	6.9	100.00%	99.74
6	10 mg/mL	7.1	100.00%	101.30
7	10 mg/mL	6.9	100.00%	99.74
8	10 mg/mL	6.9	100.00%	99.74
9	10 mg/mL	7.1	100.00%	101.30
10	10 mg/mL	7.1	100.00%	101.30
Concentration 10 mg/mL		Avg. Volume 7.02	100.00%	Mean=100.68%
Standard Deviation (NMT 1.0%) = 0.80%		Relative standard deviation (NMT 2.0%) = 0.80%		

2.4.2 Intermediate Precision

The inter laboratory precision between two qualified persons from 100% stock sample between two different analysts, see blow table 2.4.2.1 for inter laboratory precision.

Inter Laboratory Precision, table 2.4.2.1 for analyst 'A' and 'B'				
Analyst 'A'			**Analyst 'B'**	
Sample #	**Volume consumed by Dioctahedral Smectite**	**Practical Yield (%) of label claim**	**Volume consumed *DOS***	**Practical Yield (%) of label claim**
1	6.90	99.31	6.90	99.31
2	7.00	100.75	6.90	99.31
3	6.90	99.31	7.00	100.75
4	7.00	100.75	7.00	100.75
5	6.90	99.31	7.00	100.75
6	7.00	100.75	7.00	100.75
Average Volume 6.96		Mean **100.03%**	Avg. Volume **6.96**	Mean = **100.27%**
Standard Deviation (NMT 1.0%) **=0.79%**			Standard Deviation (NMT 1.0%) = **0.74%**	
Relative Standard Deviation = (NMT 2.0%) Obtained Value = **0.79%**			Relative Standard Deviation = (NMT 2.0%) Obtained Value **=0.74%**	

2.5 ACCURACY

Below statistical data of accuracy, where systemic approach states the confidence level between the values, which are known either as a predictable true value or possess well-known reference valuation. See table 2.5.1.

2.5.1 RECOVERY OF THE *DIOCTAHEDRAL SMECTITE, NEXDROL SACHET*:

Recovery of Nexdrol 3.0 g Sachet "*Dioctahedral Smectite''* (Table No.2.5.1)

S. No.	Spiked Qty.	Sample 01 Volume	Sample 02 Volume	Mean	Recovered % QTY	Practical Yield %
1	Sample 80 %	6.60	6.60	6.60	80.74%	100.92%
2	Sample 100 %	7.00	7.00	7.00	100.75%	100.75%
3	Sample 120 %	8.4	8.4	8.4	120.88%	100.74%
Relative Standard Deviation: RSD % = (NMT 2.0%) Obtained value = **0.10**						**Avg. 100.80%**

2.6 Limit of Detection (LOD)

Limit of Detection of Dioctahedral Smectite APIs easily detected at the minimum concentration of analyte detected equal to ***0.2 mg/ mL*** on visual basis.

2.7 Limit of Quantitation (LOQ)

The limit of quantitation accomplished on the concentration obtained at the level of ***1 mg / mL,*** the amount of analyte in a sample. which can be quantitatively determined with suitable precision and accuracy.

3. Acceptance criteria with results are Summarized in below table 3.1.

Table 3.1.

Parameters	Acceptance Limit	Result	Remarks
Identifications	The ***Dioctahedral Smectite*** reference standard and FPP Nexdrol 3.0 g Sachet exhibit same pink color before Titration, while after titration both API & FPP display green color.	Complies	OK
Linearity	Correlation coefficient NMT 1.0	0.9997	OK
Range	Correlation coefficient NMT 1.0	0.9992	OK
Repeatability	Standard deviation not more than 2%	0.80%	OK
Intermediate Precision	Result should reproducible by two different analysts (Analyst A,B) with standard deviation NMT 2%	A= 0.74%	OK
		B= 0.79%	OK
Accuracy	SD % between practical and theoretical determination For Assay ± 2%	0.10%	OK
Limit of detection	0.2 mg / mL Visually found	Conformed	OK
Limit of Quantitation	1 mg / mL Dioctahedral Smectite quantified	Conformed	OK

4. CONCLUSION

The Analytical Test Method Validation of *Dioctahedral Smectite''* API's, *(Nexdrol 3.0 g Sachet)* intend to be used for finished product testing. Above mentioned individual attributes were performed for *(Dioctahedral Smectite'' Nexdrol 3.0 g Sachet).*

5. REFERENCES

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