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FORMULATION AND EVALUATION OF TOPICAL SOLUTION OF TRANEXAMIC ACID AS NASAL SPRAY

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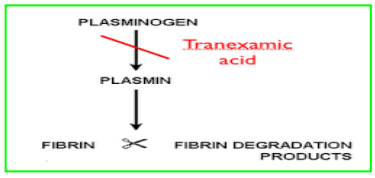
Abstract:

Tranexamic acid is an Hemostatic agent which acts by blocking the conversion of plasminogen to plasmin which is required in the formation of blood clot as shown in following diagram. It is Available in tablet, injection and Mouthwash form in market for the treatment of bleeding cases; an attempt was made to prepare and evaluate Nasal spray containing Tranexamic acid as a Active ingredient and Sodium CMC was used as mucoadhesive polymer to increase the contact time of formulation as , in nose bleeding the flow of blood is there and to avoid the washout of drug from site of action this is necessary to increase the contact time by increasing the viscosity of formulation by using the mucoadhesive polymer. and form artificial net to stop bleeding by trapping blood cells (RBC Etc.).Various formulations were prepared by using different concentrations of Sod. CMC and the best formulation were optimized by checking the spray property and contact time of each trial batch. The prepared Formulation were evaluated for their physicochemical parameters such as physical appearance, pH, Viscosity, Assay (drug content uniformity), In-vitro permeation, Spray property, In-vitro permeation, Droplet size distribution, Pump Delivery, and contact time. A 6^1 full factorial design was applied to the formulations containing different concentration of polymer . From factorial design batches (F0-F5) the batch with Good sprayability and higher contact time(F3) were considered as optimized batch. Finally it can be concluded that the nasal spray of tranexamic acid were formulated and evaluated successfully for treatment of epistaxis, Accidental and operative bleeding.



Keywords: *Tranexamic acid, Sod. CMC, Hemostatic, RP-HPLC,Epistaxis.*

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INTRODUCTION:

The Rational behind the formulation of this nasal spray is that the Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine-binding site of plasminogen. Currently, it is one of the most commonly used haemostatic drugs and is capable of reducing blood loss volume in surgical patients, Moreover, this drug has effectively reduced the blood loss volume in various surgical settings, including in traumatic haemorrhage, caesarean section, and cardiac surgeries. The tremendous Clinical trials are carried out by different Organisations to determine the efficacy of tranexamic acid applied locally to control bleeding and available on the website U.S. Library of medicine : ClinicalTrials.gov and they determined its external efficacy and the no side effect as internal medicines have the side effect of Thrombosis (Internal blood clot formation and embolism). Tranexamic acid Is now available in Tablet, Injectable, Mouthwash Dosage forms to stop bleeding and Bathing Soap (Skin whitening). The 5 % mouthwash of tranexamic acid are now recently coming into the market for the patient on which the Mouth surgery (Ex. Tooth Extraction) carried out ; the Two pharmacy also make its own Mouthwash to stop bleeding in dental surgery in patient having coagulation defects. The Monograph of Tranexamic acid Mouthwash also made available for testing by British Pharmacopoeia commission. A tranexamic acid solution can be used before a procedure to prevent bleeding in patients with bleeding disorders. The solution is used as a rinse by the patient for about 2 minutes, a half hour before a procedure. Tranexamic acid can also be used after the procedure and as needed in emergency situations. After an oral procedure a solution can be used by the patient every one to two hours to control bleeding. It should be held in the mouth by the patient and not “swished” as this can dislodge a clot. In tablet form, antifibrinolytic medications are available under different brand names. They are prescribed for patients who have blood clotting disorders and are having minor surgery. In the case of oral surgery however, taking a tablet is not ideal for these patients. Topical administration of tranexamic acid with a rinse inhibits clot breakdown locally while minimizing systemic effects. For patients who have coagulation disorders and are on medications like warfarin, reducing systemic effects can be crucial. A tranexamic acid mouth rinse results in a lower plasma concentration than a tablet while effectively controlling bleeding.

The Rationale behind use of Sodium CMC was; It is found as mucoadhesive polymer and tremendously used in to the Eye drops (Artificial Tears) Manufacturing . So I decided to use this polymer in my formulation to increase the contact time of formulation as , in nose bleeding the flow of blood is there and to avoid the washout of drug from site of action this is necessary to increase the contact time by increasing the viscosity of formulation by using the mucoadhesive polymer.

MATERIALS AND METHODS:

Table no.: 01: List Of Chemicals:

Sr. No.	Name of the Chemicals	Category	Manufacturer / Supplier
1	Tranexamic Acid	API	Shilpa Medicare Limited Raichur ,Karnataka
2	Sodium CMC	Polymer	Lucid Colloids Ltd.
3	Sodium Metabisulphite	Antioxidant	Halogens Tundav,Vadodara
4	Monopotassium Phosphate	Buffer system	Halogens Tundav,Vadodara
5	Disodium Hydrogen Phosphate	Buffer system	Halogens Tundav,Vadodara
6	Sodium Methyl Paraben	Preservative	Nebula Healthcare Ankhol, Gujarat.
7	Methanol (HPLC)	Solvent	Merck Life sciences Mumbai
8	Triethylamine (HPLC)	Solvent	SDFCL Mumbai
9	Perchloric Acid 70 %	Reagent	Loba Chemie Pvt Ltd.

Table No.2: List of Instruments:

Sr. No.	Name of the Instrument	Model/Make
1	Analytical weighing balance	Shimadzu (AUX220)
2	UV Vis-Spectrophotometer	Shimadzu (UV-1800)
3	ATR spectrophotometer	Shimadzu, Japan
4	TOC Analyzer	Shimadzu
5	Magnetic Stirrer	Remi Equipments, Mumbai.
6	Sonicator	Citizen.
7	Hot Air Oven	Thermolab, Mumbai
9	Viscometer	Brookfield viscometer
10	Digital PH meter	Toshniwal instruments Ajmer
11	Stability chamber	Thermolab, Mumbai.
12	Franz Diffusion Apparatus	Orchid
13	HPLC	Agilent Technologies (1120 Compact LC)
14	Melting point Apparatus	Thermocal

Preformulation Study:

Identification tests:

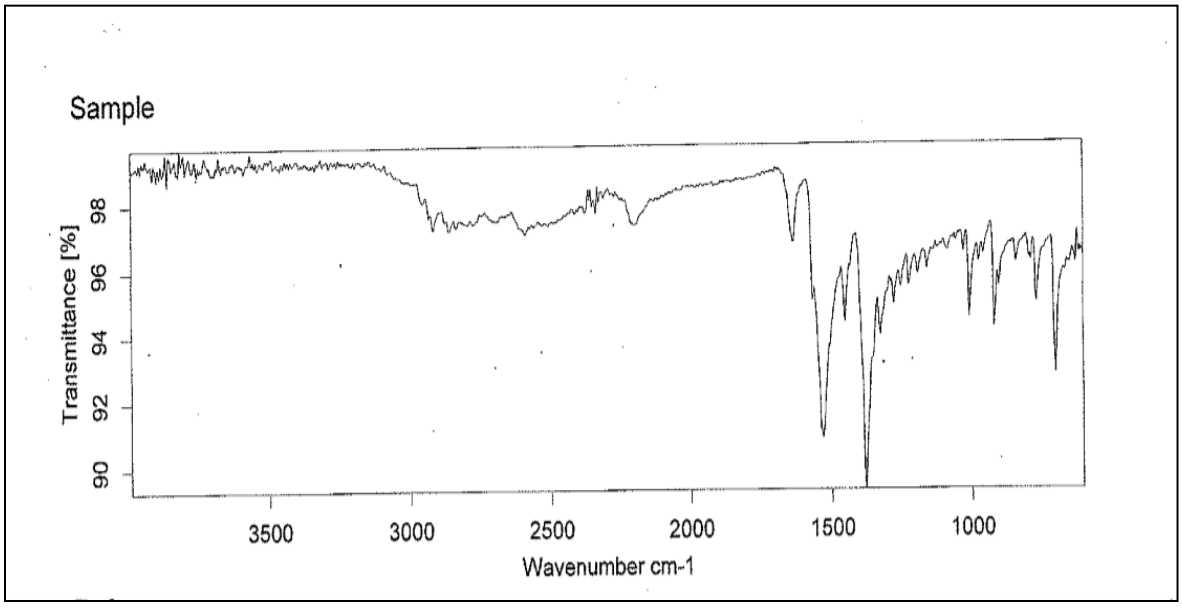
Identification Test	Pharmacopoeial Standard	Observed Result
Appearance	Crystalline	Crystalline
Colour	White Or Almost White	White
Odour	Odourless	Odourless

Solubility:

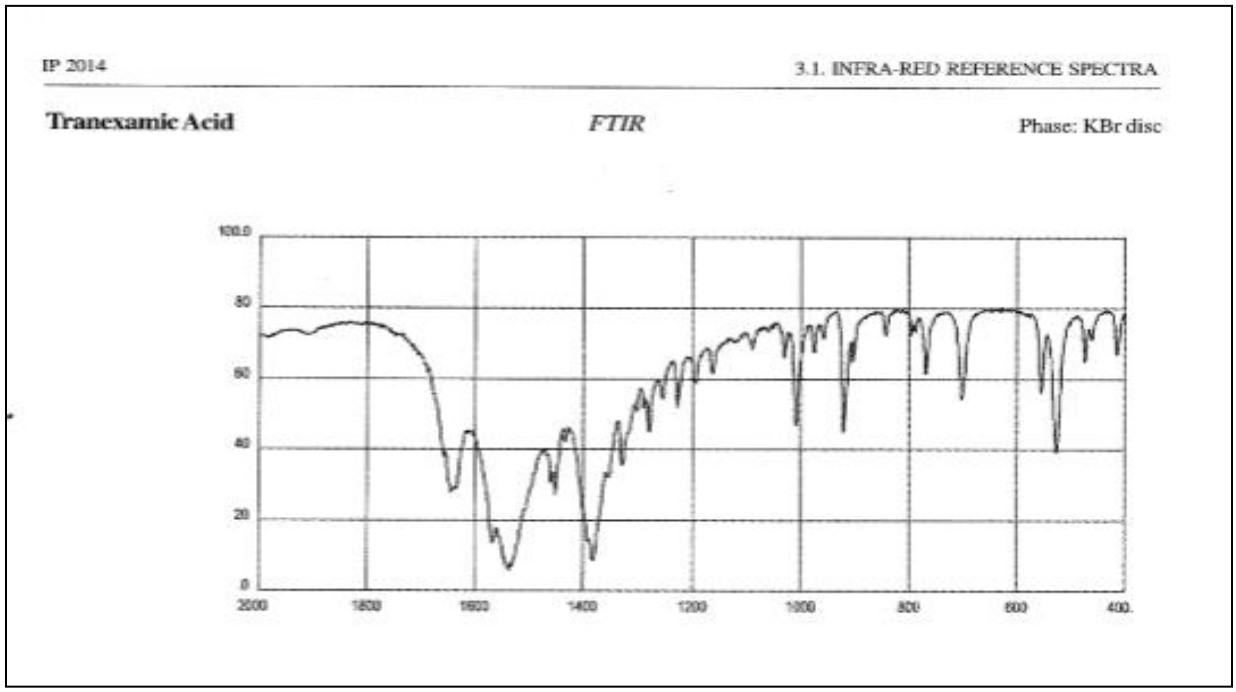
Solvent	Pharmacopoeial Standard	Observed Solubility
Water	Freely soluble	Freely soluble
Phosphate Buffer pH 6.8	Freely soluble	Freely soluble
Glacial Acetic Acid	Freely soluble	Freely soluble
Acetone	Practically Insoluble	Practically Insoluble
Ethanol (96 %)	Practically Insoluble	Practically Insoluble

FTIR Spectrophotometric Analysis:

The infrared absorption spectrum, Of sample matched with the spectrum given into the Indian Pharmacopoeia and found identical to each other.



FTIR Spectra of Tranexamic acid



IR Spectra of Tranexamic acid As specified in IP 2014

Calibration curve of Tranexamic acid by RP-HPLC

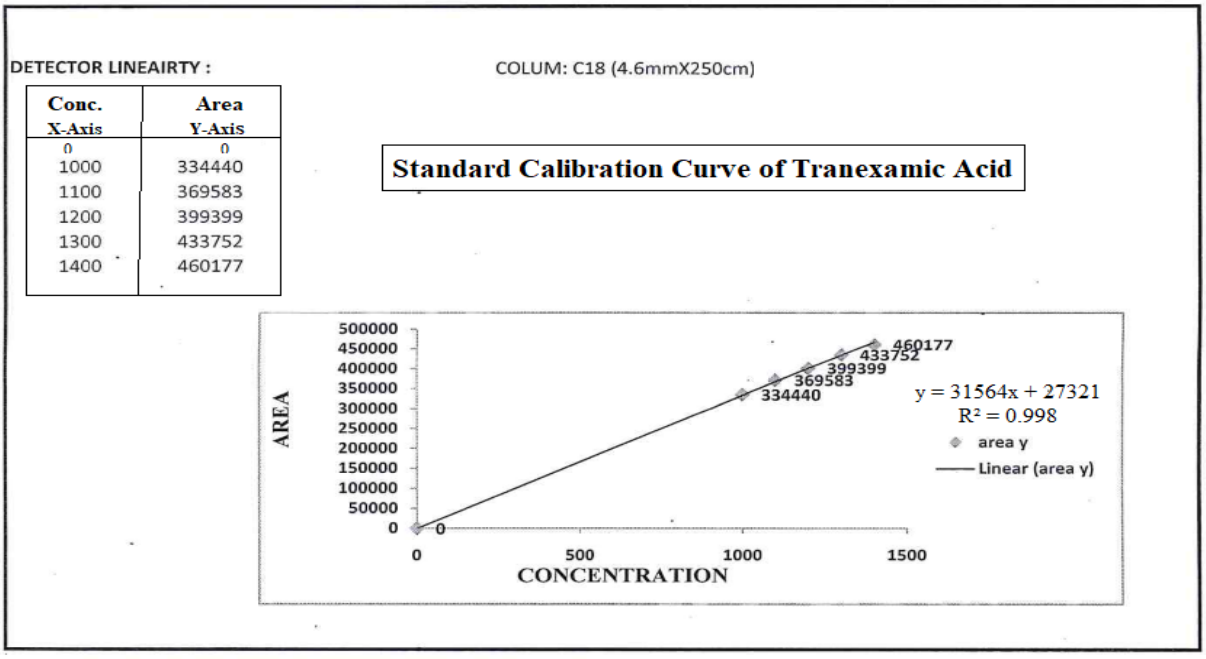


Table No: 3 Factorial design of batches for Optimization:

Formulation Ingredients	Formulation Codes					
	F0	F1	F2	F3	F4	F5
Tranexamic Acid	5 %	5 %	5 %	**5 %**	5 %	5 %
Sodium CMC	0.0 %	0.1 %	0.3 %	**0.5 %**	0.7 %	0.9 %
Sodium Metabisulphite	0.1 %	0.1 %	0.1 %	**0.1 %**	0.1 %	0.1 %
Monopotassium Phosphate	0.0301 %	0.0301 %	0.0301 %	**0.0301 %**	0.0301 %	0.0301 %
Disodium Hydrogen Phosphate	0.050 %	0.050 %	0.050 %	**0.050 %**	0.050 %	0.050 %
Sodium Methyl Paraben	0.2 %	0.2 %	0.2 %	**0.2 %**	0.2 %	0.2 %
Purified Water	Q.s.to 100 %	Q.s.to 100 %	Q.s.to 100 %	**Q.s.to 100 %**	Q.s.to 100 %	Q.s.to 100 %

General Procedure for Preparation of Nasal Spray:

1) Manufacturing of Bulk solution :

- 80% Of vehicle / solvent (Purified Water) are taken into Mfg. Tank and require to Flush Nitrogen as inert gas for 15 min. to remove dissolved gases from vehicle.
- Add and dissolve the Preservative **(Sodium Methyl Paraben)** into above solution.
- Add and Dissolve the Antioxidant **(Sodium Metabisulphite)** into it and stir well continuously with continue Nitrogen spurging into solution with SS Tubing, tube should reach upto the Bottom of Mfg. Tank.
- Add and Dissolve the Buffer contributing ingredients **(Monopotassium Phosphate** and **Disodium Hydrogen Phosphate).**
- Check the pH Of above solution ,it should be near to the pH at which active material stable.
- Then add and Dissolve Active Material **(Tranexamic Acid)**and stir well.
- Then add and dissolve the any other Viscosity modifying ingredient **(Sodium CMC)** ; it is good to make slurry into small amount of vehicle at 45 to 50 ^{0}C and then transfer to the main Batch with stirring.
- The remaining 20% Vehicle will be used for the Rinsing purpose and volume makeup.
- Make up the final volume with remaining Solvent/vehicle.

2) Filling Of Manufactured Bulk into Spray Bottle :

- Plastic Squeeze Type plastic Spray bottle are used for the Filling of bulk supplied from SSF Plastic Pvt. Ltd. Bhimpore, Dalama, Daman and Diu.
- Supplied Bottles are washed before filling and dried.
- The manufactured Bulk was filled into the Squeeze type spray bottle (10ml) with pre and post Nitrogen Flushing and instantly the Straw type plug and cap was fixed .

EVALUATION OF NASAL SPRAY OF TRANEXAMIC ACID:

1) Description of formulated solution.
2) E.g. Colour, Odour, State etc.
3) Viscosity
4) Density of formulation.
5) Sprayability / Spray Property
6) pH of Formulation
7) Assay
8) *In-vitro* permeation.
9) Droplet size distribution.
10) Pump Delivery.
11) Skin Irritation Study.
12) Contact time / Mucoadhesive strength.
13) Stability study of optimized formulation of Tranexamic Acid.

Table 4. Evaluation Table:

Sr. No	Formulation Code	Description Of Formulation	Viscosity (Cp)	Density (gm/ml)	pH
01	F0	Clear , Colourless Solution	1	1.01	7.05
02	F1	Clear , Colourless Solution	21.55	1.02	7.1
03	F2	Clear , Colourless Solution	37.2	1.02	7.2
04	F3	Clear , Colourless Solution	63.5	1.04	7.2
05	F4	Clear , Colourless Solution	120.3	1.05	7.3
06	F5	Clear , Colourless Solution	200.1	1.05	7.2

Assay of formulations by RP-HPLC

$$\text{Assay By HPLC} = \frac{\text{Area of Standard (R.M)}}{\text{Area of Test / Sample}} \times \underbrace{\frac{\text{Std. Wt.}}{\text{Dil. Vol.}} \times \frac{\text{Vol. taken from 1st}}{\text{Dil. Vol.}}}_{\text{Dilutions of standard}} \times \underbrace{\frac{\text{Dil. Vol. upto}}{\text{Sample vol. taken}} \times \frac{\text{Dil. Vol.}}{\text{Vol. taken from 1st}}}_{\text{Dilutions of Test}} \times \frac{\text{Assay of Std. (R.M)}}{100}$$

Table 5. Evaluation Table:

Sr. No.	Formulation Code	Area		Assay (mg/ml)	Assay (%)
		Standard (1000 ppm)	Test / Sample		
01	**F0**	334440	334849	48.19	**96.38**
02	**F1**		334010	48.31	**96.62**
03	**F2**		333982	48.32	**96.64**
04	**F3**		330123	48.88	**97.76**
05	**F4**		333150	48.44	**96.88**
06	**F5**		330515	48.82	**97.64**

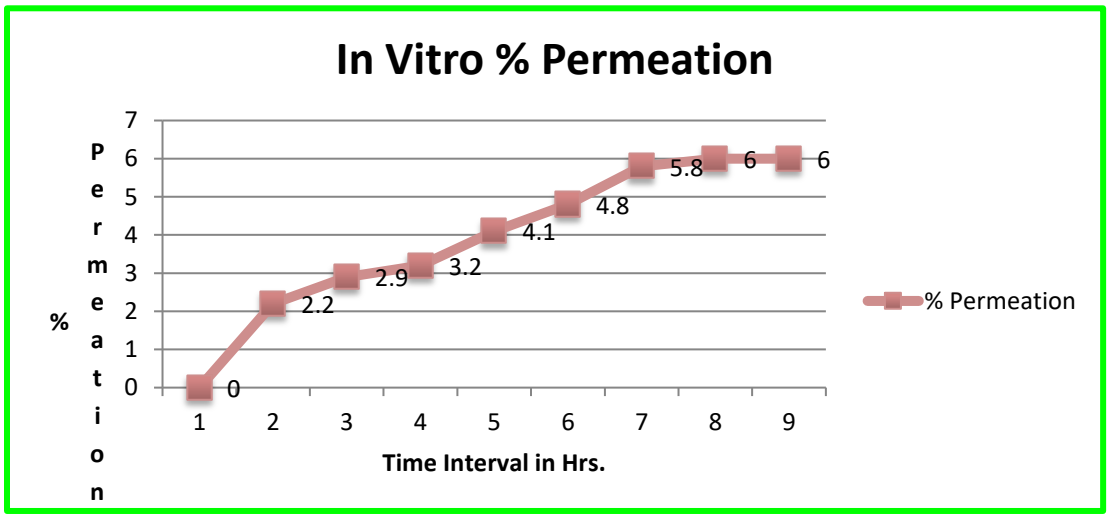
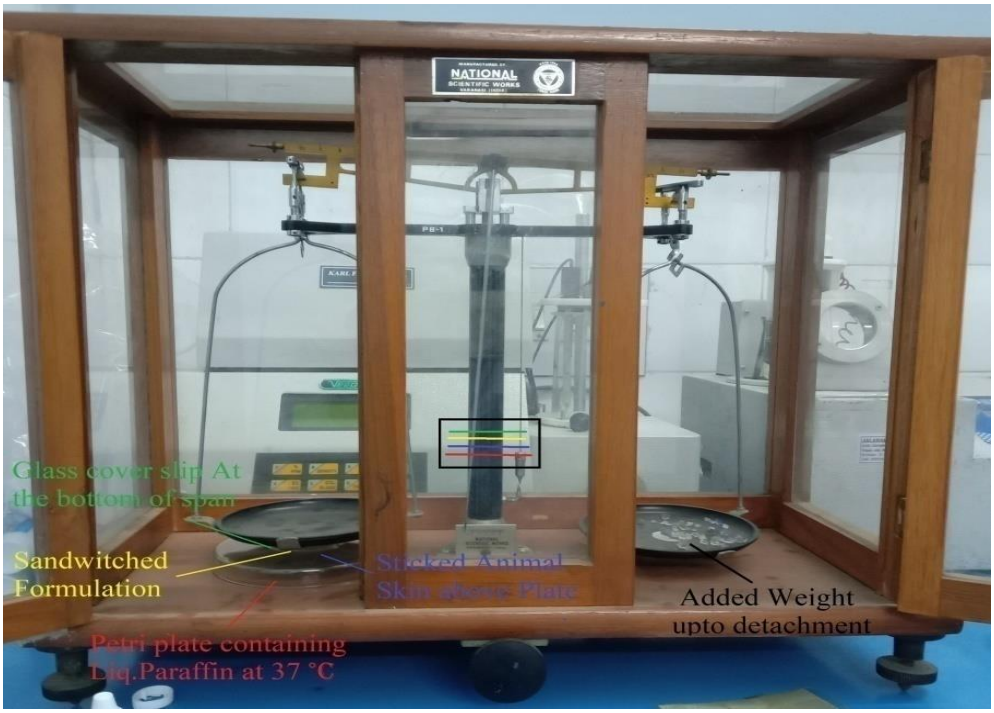


Table 6. Evaluation Table:

Sr. No.	Formulation Code	Mucoadhesive Strength (gm)
01	F0	0.89
02	F1	1.10
03	F2	1.45
04	F3	1.79
05	F4	2.91
06	F5	3.89



Pump Delivery :

Table 7. Evaluation Table:

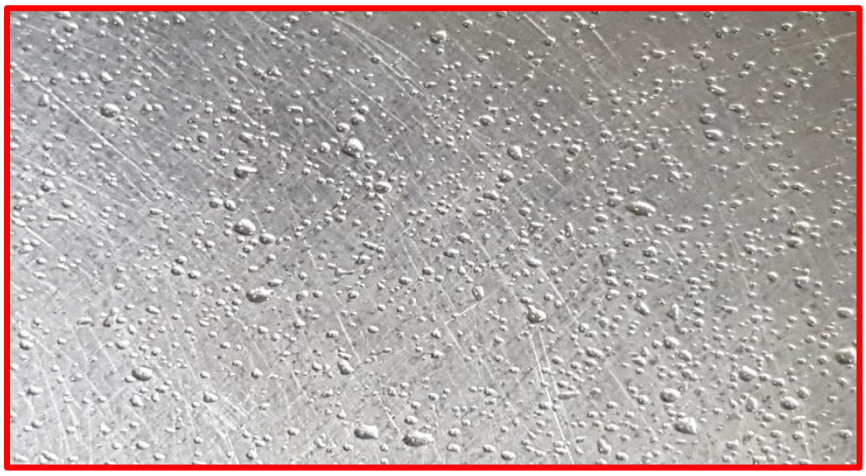
Sr. No.	Initial Gross Wt of spray	Gross Wt. After Spray Delivery	Net Volume (Gm) Ejected
1	28.21	27.76	0.45
2	27.76	27.39	0.37
3	27.39	27.09	0.30
4	27.09	26.78	0.31
5	26.78	26.45	0.33
Mean of pump delivery			0.35

- **Droplet Size Distribution :**

Table No 8.: Droplet Size Distribution

Height (cm)	Size of Droplet (mm)										Mean
	1	2	3	4	5	6	7	8	9	10	
3	1	0.41	1	0.45	1	1	0.83	0.87	1	1	0.97
6	0.15	1	1	0.75	1	1	0.95	0.91	1	84	0.86
10	1	0.87	1	0.83	1	0.38	1	0.70	1	1	0.88
Mean Droplet Size											**0.9**

The droplet size ejected by formulation was bigger that is important in case of Bleeding to deliver more formulation.



STABILITY STUDIES:

Table 9. Evaluation Parameters of Formulation F3 during stability study

Sampling Time Interval (Month)	Description Of Formulation	Viscosity (Cp)	Density (gm/ml)	pH	Assay (%)
Initial	Clear , Colourless Solution	63.5	1.04	7.2	97.46
1	Clear , Colourless Solution	64.2	1.02	7.1	96.38
3	Clear , Colourless Solution	63.8	1.03	7.2	98.62
6	Clear , Colourless Solution	64.5	1.04	7.3	96.64

RESULT AND DISCUSSION:

The aim of present investigation was to develop Formulation Of Tranexamic Acid Nasal Spray For Treatment Of Intranasal Bleeding and blood loss in Epistaxis and Accidental conditions. The pre-formulation study was performed for both drug and excipients. The compatibility study between Tranexamic Acid and excipients was ascertained by FTIR and Assay of Physical Mixture. The Different Batches was prepared and concentrations of Excipients were optimized. Sodium CMC was used as Polymer to increase the contact time of formulation with damaged skin. A 6^1 full factorial design was applied to Optimize concentration of Sodium CMC, The Modified balance was used to study the contact time of developed formulations. The Formulation were evaluated for parameters such as Description of formulated solution, E.g. Colour, Odour, State etc. Then Viscosity, Density of formulation, Sprayability / Spray Property, pH of Formulation, Assay, Skin Irritation Study, *In-vitro* permeation, Droplet size distribution, Pump Delivery, Contact time / Mucoadhesive strength etc. The 6 months Stability study of optimized formulation of Tranexamic Acid was carried out and found stable.

CONCLUSION:

- Optimized Nasal spray (F3) showed the desired characteristics that should have for intranasal products.
- Optimized formulations (F3) have Good Sprayability and the longer contact time; which may not washout during flow of blood.
- Optimized formulations (F3) Showed the same Sprayability in comparative study with Marketed formulation.
- As mentioned above the F3 batch was Optimised due to its Good Sprayability and longer contact time.
- It is found that as concentration of Sod. CMC Increases the Spray property decreases so lower concentration having good sprayability batch was optimized.
- The no compatibility issue was observed in batches as per Stability analysis data.
- From the result of 21 Day Skin irritation study; it is concluded that the no Side effects of formulation was there.
- Finally it can be concluded that the Formulation Of Tranexamic Acid Nasal Spray For Treatment Of Intranasal Bleeding and blood loss in Epistaxis and Accidental conditions was Successfully developed.

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REFERENCES:

1. British Pharmacopoeia 2015; The Department Of Health, Social Services And Public Safety; Published by British Pharmacopoeia Commission London; Volume 3 , 5 pg.no.398,1247-1249
2. Indian Pharmacopoeia 2014 , Government of india , Ministry of health and family welfare ; published by 'The Indian Pharmacopoeia commission Ghaziabad' ,Page no.602,1901-1904
3. USP 40 - NF 35 The United States Pharmacopeia and National Formulary 2017; published by the United States Pharmacopeial Convention;Maryland, United States Pg. No. (Online version)
4. Noble S, Chitnis J. Case report: use of topical tranexamic acid to stop localised bleeding. Emerg Med J. 2013;30(6):509-510.
5. Brian OS , James DB, Anil KD et.al.UICC Manual of clinical oncology ,Ninth Edition;Published by John wiley and sons Ltd. 2015 U.K. page no. 179
6. Sabrina T ,Klaus W , Rene S , et.al. ;Analytical Challenges and Regulatory Requirements for Nasal Drug Products in Europe and the U.S.Pharmaceutics 2014, 6:195-219
7. Tripathi KD. Essential of Medical Pharmacology, 6th edition 2008, Jaypee Brothers Medical Publishers (p) ltd. Page.No.581-593.
8. Coetzee M. The use of topical crushed tranexamic acid tablets to control bleeding after dental surgery and from skinulcers in haemophilia. Haemophilia. 2007;13(4):443-444.
9. S. Lungare, J. Bowen, R.K.S. Badhan;Development and Evaluation of a Novel Intranasal Spray for the Delivery of Amantadine. Journal of Pharmaceutical Sciences, 2016. 105(3) pp. 1209–1220.
10. Utkewicz M, Brunetti L, Awad N. Epistaxis complicated by rivaroxaban managed with topical tranexamic acid. Am J Emerg Med. 2015;33(9):1329.5-7.
11. Sanjay D, Beduin M, Bhasakar M, et.al.;Nasal drug delivery: An approach of drug delivery

through nasal route;Pelagia Research Library ,Der Pharmacia Sinica, 2011, 2 (3): 94-106
12. Zahed R ,Moharamzadeh P, Alizadeharasi S, et.al ; A new and rapid method for epistaxis treatment using injectable form of tranexamic acid topically: a randomized controlled trial; Am J Emerg Med. 2013 Sep;31(9):1389-92
13. Scott D. Trick of the Trade: Topical Tranexamic Acid Paste for Hemostasis. Aliem: Academic life in emergency medicine February 17th, 2016. (https://www.aliem.com/2016/02/trick-trade-topical-tranexamic-acid-paste-hemostasis/)
14. Ambados F. Letter to the editor. Preparing tranexamic acid 4.8% mouthwash.Australian Prescriber. 2003;26:75-77.
15. Ali s ; 'Tranexamic acid is more effective than nasal packing for treatment of Epistaxis ;NEJM Journal watch, 2017 (https://www.jwatch.org/na45649/2017/12/08/tranexamic-acid-more-effective-nasal-packing-treatment)
16. Chhajed S, Sangale S ,Barhate SD. Advantageous Nasal Drug Delivery System: A Review; IJPSR, 2011; Vol. 2(6): 1322-1336
17. Upadhyay S, Parikh A, Joshi P, et.al. Intranasal drug delivery system- A glimpse to become maestro;Journal of Applied Pharmaceutical Science 01 (03); 2011: 34-44
18. Patatanian E, Fugate S. Hemostatic mouthwashes in anticoagulated patients undergoing dental extraction. Ann Pharmacother. 2006; 40(12):2205-2210.
19. Menaka M, PandeyVP; Formulation Development and Evaluation of Cinnarizine Nasal Spray; International Journal of Pharma Research and Health Sciences; Volume 2 (4), 2014, Page-339-346
20. Abraham Klepfish, Alain Berrebi, Ami Schattner, Intranasal Tranexamic Acid Treatment for Severe Epistaxis in Hereditary Hemorrhagic Telangiectasia; Arch Intern Med. 2001;161(5):767-769
21. Joseph J, Martinez-DP,Bellorini J, et.al. Tranexamic acid for patientswith nasal haemorrhage (epistaxis).CochraneDatabaseofSystematicReviews 2018, Issue 12. Art.No.: CD004328.
22. https://www.jwatch.org/na45649/2017/12/08/tranexamic-acid-more-effective-nasal-packing-treatment 02/03/2019 2:15 pm
23. Bhuva F, Patel LD. Xylometazoline nasal spray solution: novel composition used for treatment of nasal congestion. MOJ Drug Des Develop Ther. 2018. 2(5); 246–255.
24. https://en.wikipedia.org/wiki/Nasal_administration 03/03/2019 9:43 am.
25. https://en.wikipedia.org/wiki/Tranexamic_acid 03/03/2019 10:50 am.
26. Thorat S, Formulation and Product Development of Nasal Spray: An Overview ;Sch. J. App. Med. Sci., Aug 2016; 4(8D):2976-2985
27. Oral and Dental Expert Group. Therapeutic guidelines: Oral and Dental. Etg46 November 2015 Copyright 2016 HealthSmart Pharmacy Carlton (https://www.dhsv.org.au/__data/assets/pdf_file/0005/84605/Tranexamic-acid-mouthwash.pdf)
28. Hughes D. Topical Tranexamic Acid for Epistaxis or Oral Bleeds – R.E.B.E.L. EM – Emergency Medicine Blog. R.E.B.E.L. EM – Emergency Medicine Blog.(http://rebelem.com/topical-tranexamic-acid-epistaxis-oral-bleeds/Published July 14, 2014.)
29. Milne K, Hanel E: Sunday, Bloody Sunday (Epistaxis and Tranexamic Acid).The Skeptics Guide to Emergency Medicine.(http://thesgem.com/2013/11/sgem53-sunday-bloody-sunday-epistaxis-and-tranexamic-acid/ Published November 18 2013.)
30. U.S.National library of medicine ;Topical Intranasal Tranexamic Acid for Epistaxis in the Emergency Department (https://clinicaltrials.gov/ct2/show/study/NCT02930941)
31. Zahed R , Mousavi Jazayeri MH , Naderi A , et.al .Topical Tranexamic Acid Compared With Anterior Nasal Packing for Treatment of Epistaxis in Patients Taking Antiplatelet Drugs: Randomized Controlled Trial,AcadEmerg Med. 2018 Mar;25(3):261-266
32. Adam R, Andrew A, Andy Bet.al. 'Novel use of tranexamic acid to reduce the need for Nasal Packing in Epistaxis (NoPac) randomised controlled trial: research protocol. "BMJ Open" medical journal, feb.2019 (https://www.researchgate.net/publication/331151245_Novel_use_of_tranexamic_acid_to_reduce_the_need_for_Nasal_Packing_in_Epistaxis_NoPac_randomised_controlled_trial_research_protocol)
33. Yisheng W , James AL ,Martin TC.'Role of topical tranexamic acid in hemostasis of locally advanced basal cell carcinoma' Journal of the American Academy of Dermatology · April 2016 JAAD Case Reports 2016;2:162-3.2352-5126
34. Senthil Kumar K , Varma M, Vudaykiran A. 'Nasal Drug Delivery System - An Overview' ; International Journal Of Pharmaceutical And

Chemical Sciences , Vol. 1 (3) Jul-Sep 2012:1358-1368
35. Rahusuddin, Sharma P, Garg G; Review on Nasal Drug Delivery System with recent advancement; Int J Pharm Pharm Sci, Vol 3, Suppl 2, 2011, 6-1 1
36. Alagusundaram M, Chengaiah B, Gnanaprakash K; Nasal drug delivery system - an overview; Int. J. Res. Pharm. Sci. Vol-1, Issue-4, 2010, 454-465
37. Barbara C, Muhammad G, Mohammed M; Nasal Drug Delivery Systems: An Overview; American Journal of Pharmacological Sciences, 2015, Vol. 3, No. 5, 110-119
38. Christoph B, Katja S, Christian S; Nasal Drug Delivery in Humans; Curr Probl Dermatol. Basel, Karger, 2011, vol 40: 20–35