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Sublingual Delivery Of Trimethyl Chitosan Chloride (Tmc) Polymeric Drops For The Quick Management Of Pain

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ABSTRACT

The goal of this study was to develop and characterize a trimethyl chitosan chloride (TMC) polymeric drops system which can deliver drug sublingually for quick management of pain. Ketorolac tromethamine (KT) is a nonsteroidal anti-inflammatory drug utilized for the management of moderate to severe pain at the opioid level. The sublingual polymeric drops were developed by utilizing TMC alongside the distinctive proportion of sweeteners and excipients. The TMC with quaternization of 37.03%, a derivative of chitosan was synthesized by two-stage reductive methylation procedure to enhance the solvency and penetrability. All the fifteen (F1-F15) formulations were characterized for taste, pH, viscosity and drug content uniformity. The optimized formulation F15 (pH=5.460.26; viscosity=23.660.57; drug content=98.78%) was chosen for further studies. The drug, polymer and excipient were checked for compatibility with FTIR, DSC, and XRD. The ex vivo permeation demonstrated that 94.70 % of drug penetrated within 30 min. The in vivo study on rat model & statistical analysis was observed for analgesic activity showing satisfactory results whereas stability study predicted slightly acceptable change in properties. From the above research examination and information investigation, it can be presumed that developed TMC polymeric drops can convey a fitting measure of medication sublingually for quick management of pain.

KEYWORDS: Trimethyl chitosan chloride, Ketorolac tromethamine, Box-Behnken Designed, Sublingually, Quick management of pain.

1. INTRODUCTION

The attempt to understand pain represents one of the oldest challenges in the history of medicine and Pharmaceutical science. The pain has a valuable role in medical action, as the symptom par excellence and, therefore, as a precious and meaningful tool. An important step forward in the scientific characterization of pain has been taken with the Sherrington's definition of the phenomenon as "the psychical adjunct of an imperative, protective reflex" and the description of its neurophysiological aspects **[1]**. Ketorolac (KT) is a potent water soluble pain relieving drug utilized for the management of moderate

to extreme pain, incorporating that connected with stomach, gynaecologic, oral, orthopaedic, or urologic postoperative surgery **[2]**, alongside having mellow antipyretic action **[3]**, It has likewise been utilized for the management of instinctive agony connected with disease, and those of intense renal colic pain connected with injury **[4, 5]**. The exploration examination uncovered that KT has a pain relieving action of 36 times more intense than phenylbutazone, roughly twice as strong as indomethacin, and 3 times more powerful than naproxen **[6]**. It is accessible at present as tablets, ophthalmic arrangements, and injections. It is managed orally, intramuscularly, intravenously and as ophthalmic readiness. KT was the primary injectable non-steroidal pain relieving drug affirmed for the administration of intense agony **[7]**. On intramuscular administration; it engenders analgesia commensurable to that of intramuscular (i.m.) doses of meperidine, pentazocine, or morphine **[8]**. Its predominant pain relieving action **[9, 10]**, safety, non-narcotic property and general cost adequacy when contrasted with opiates, it is suggested as a suitable alternative for opioid analgesics (morphine and meperidine) **[11, 13]**. The parenteral administration of KT (i.m. and i.v.) causes incompliance and obtrusive conveyance for a sensibly longer timeframe (5-6 days in serious torment conditions connected with significant surgery). On the other hand, the oral conveyance of KT conquers the restriction connected with intrusive conveyance, with the bioavailability of 90% with low hepatic first-pass disposal **[14, 15]**. Then again, the oral organization of KT is constrained because of broad gastric ulceration and puncturing **[16]**.

The present research was planned to develop a sublingual Trimethyl Chitosan Chloride (TMC) polymeric drop system with enhanced compliances and bioavailability and beating the issues i.e. gastric ulceration connected with oral dosing of KT. The sublingual drops can proficiently use for management and better treatment of pain. Potential advantages of the sublingual route include good permeability, rapid absorption, acceptable bioavailability faster onset of action and increased bioavailability It might be an alternate route for patients who can not swallow the oral dose form of drug **[17, 18]**. While TMC triggers the opening of the tight convergences, therefore encouraging the paracellular transport of medication. The TMC involves extraordinary solubility at all pH esteem and improved penetration upgrading property over chitosan polymer **[19, 20]**.

2. MATERIALS AND METHOD

Ketorolac tromethamine (KT) was supplied as generous gift sample by Symed Lab (Hyderabad, India). N-methyl-2-pyrrolidinone (NMP) was purchased from Fischer Scientific (Mumbai, India). Chitosan from shrimp shells (degree of deacetylation ≥ 75%), Sodium iodide, N-methyl-2-pyrrolidinone (NMP), sodium hydroxide, methyl iodide, diethyl ether and sodium chloride, sodium citrate, methyl & propyl paraben, sucrose, sorbitol, sodium saccharin were purchased from Himedia, (Mumbai, India). Ethanol was purchased from SD Fine Chemicals (Mumbai, India). Double deionized water was obtained by a Ranchem (New Delhi, India) and was employed in various protocols. All other chemicals and solvents used in various studies were of analytical grade and were consumed as such.

Method

Synthesis of TMC

For the synthesis of TMC, a two-step reductive methylation process was adopted described by Sieval et al., 1998 with slight modification to improve the solubility & permeability. Firstly, chitosan (2 g) and sodium iodide (4.8 g) were dissolved in 1-methyl-2-pyrrolidinone (80 ml) by stirring for 30 min in a water bath at 60°C. Sodium hydroxide (11 ml, 15% w/v) and methyl iodide (11.5 ml) were added to the solution and stirred for 1 h. The product was precipitated using ethanol and diethyl ether and isolated by centrifugation. The precipitate was washed with ethanol: ether 3:1 (30ml x 3) (21). For second step synthesis, the initial precipitate was again dissolved in 1-methyl-2-pyrrolidinone (80 ml) with sodium iodide (4.8 g). Once dissolved methyl iodide (7 ml) and sodium hydroxide (11 ml, 15% w/v) were added and stirred in a water bath at 60 °C for 30 min. An additional 2 ml of methyl iodide and 0.6 g of NaOH pellets were also added and left for 1h stirring. The material produced was washed and isolated as before. At the final step of the synthesis, the product was dissolved in NaCl solution (40ml, 10%) and stirred overnight. On subsequent precipitation with the two solvents and centrifugation, the material was dissolved in 40 mL of deionized water and dialyzed for 72 h before freeze-drying **[21, 22]**.

Preparation of TMC Polymeric Sublingual Drops

The TMC polymeric drop was prepared using method described by Henwood GA, 2009 (for preparation of sublingual solution) with slight modification. Each of the ingredients was weighed under ambient conditions. Methylparaben and propylparaben were dissolved in alcohol, and the resulting solution was added to the first part of water containing citric acid. This mixture was stirred with TMC until it completely dissolved; it was then filtered and used further. To this solution, KT was added, which was stirred until all had dissolved. Next, sweeteners were added and the solution was stirred until it appeared homogenous. Sufficient water was added to bring the total volume to 10 ml & dispensed **[23, 24, 25, 26]**.

3. CHARACTERIZATION AND EVALUATION STUDIES

Identification of Tromethamine Salt by Thin Layer Chromatographic (TLC)

TLC is one of the basic analytical techniques used for higher separation efficiencies, shorter analysis time and lower amount of mobile phase required. Presence of tromethamine salt was estimated using TLC technique **[31]**.

Partition Coefficient

For determination of Partition coefficient of Ketorolac tromethamine shake-flask method was utilized. Accurately weighed drug equivalent to 10 mg was taken and dissolved in a volumetric flask (25ml) containing 10 ml each of n-octanol and buffer phase **[33, 34]**.

Solubility

The solubility of KT was estimated by utilizing saturation shake-flask Method. For solubility study of KT, a definite quantity of drug was dissolved in 1 ml of each selected Solvent system (Methanol, Ethanol, Acetone, Phosphate buffer pH 6.8, Phosphate buffer pH 7.4) at room temperature (252°C). An increment of drug was added to each test tube until undissolved particles are seen at saturation point. Then the

solvent was filtered and drug in solvent was analyzed by UV spectrophotometer (UV 1800 Shimandzu, Japan) and concentration was determined in mg/ml **[35]**.

Drug Content Uniformity

The drug content uniformity of formulation was determined by taking accurately measured volume of polymeric drops (equivalent to 10 mg of drug) in a volumetric flask and dissolving in 50 ml of phosphate buffer (pH6.8) with stirring for 10 min on a magnetic stirrer. The solution was filtered using a 0.45-µm nylon filter, and after suitable dilution, the drug content was determined using UV-Visible Spectrophotometer-1800 (Shimadzu, Japan) **[38]**.

FT-IR Spectroscopy

FTIR spectra of TMC polymer was estimated by KBr pellet technique to confirm the quaternization of chitosan. The spectra were analyzed for chitosan and TMC to determine the characteristic peaks acquired to the quaternized polymer **[39]**.

1H NMR Spectroscopy

1H NMR is one of the most accurate methods for estimating the degree of deacetylation and degree of substitution of the chemically modified polymer. The synthesized TMC was analyzed by ^{1}H-nuclear magnetic resonance (NMR) spectroscopy. The ^{1}H NMR spectra of chitosan and TMC were acquired at 353 K by using a 200 MHz spectrometer (AV-400, Brucker, Japan**) [40]**.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of the drug and the polymers were obtained using differential scanning calorimeter (DSC-60, Shimadzu, Tokyo, Japan; from Dept. of Pharm. Science and Technology, Birla institute of technology, Mesra Ranchi). All the samples were placed in a pre-weighed stainless steel pan and sealed carefully with a sealer supplied by the manufacturer. The sealed pan was weighed to obtain the sample mass. Another sealed empty stainless steel pan was used as the reference. The instrument was calibrated using the melting temperature and enthalpy of indium **[39, 40]**.

X-ray diffraction (XRD) Study

The determination of the crystalline state of the drug in the drug delivery system is essential due to the probability of change in solid state of the drug during the process, and such changes may, in turn, impact the drug release properties. The solid state properties of the drug are studied by X-ray powder diffraction technique (XRD**) [39, 40]**.

Ex Vivo Permeation Studies

Collection and Preparation of Goat Buccal Tissue. The buccal mucosa is fundamentally the same as the sublingual mucosa, so in this study, goat buccal mucosa was utilized to check the permeation of medication through the mucosa by utilizing a Franz diffusion cell at 37 ± 0.5°C. Goat buccal mucosa was obtained from a local slaughter house and was used within 2 h of slaughter. The tissues were preserved in cold phosphate buffer system **[40]**.

In vivo studies

The In vivo studies were carried out on healthy adult male Albino Wistar rats weighing 250-300 gm. The animals were procured from SLT Institute of Pharmaceutical sciences, Departmental animal house. Animals were housed in polypropylene cages (32 X 24 X 16) with stainless steel grill top at a constant temperature (24±2°C), 65% relative humidity with 12:12 hours light and the dark cycle was followed **[43, 44]**.

Stability Study

Stability testing provides authentication of the quality of the drug product with times under the influence of environmental factors such as light, pressure, temperature, etc. which enables recommended storage condition retest periods and shelf life to be established to secure the product. The processes of optimization of various batches were based on the pH, viscosity, clarity, content uniformity & taste was evaluated **[41, 42]**.

RESULTS AND DISCUSSION

Analytical data

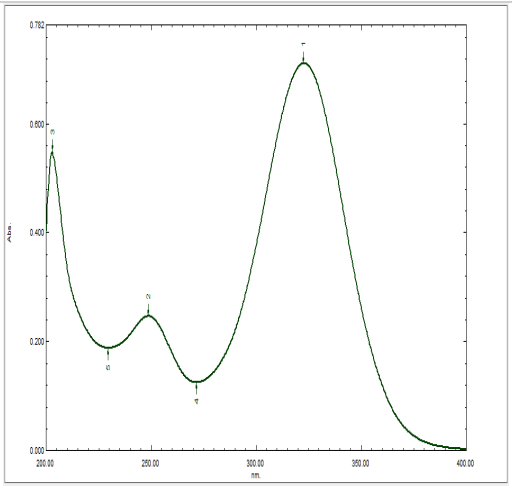
Standardization by UV Spectroscopy

For the quantitative estimation of KT in the formulation a calibration curve was prepared in phosphate buffer pH 6.8. The overlain spectrum of KT shows maximum absorbance at 322 nm hence this wavelength was selected for estimation and preparation of calibration curve. Linearity obeyed in the range of 5-50 µg/mL with the correlation coefficient 0.999. The absorbance was listed (Table 1) and standard plot of KT was shown (Figure 1). The KT sample was scanned in the spectrum mode and the overlain spectra were recorded in UV range 200-400 nm. From the overlain spectra of the drug, maximum absorption (λ_{max}) was observed at wavelength 322 nm.

SN.	CONCENTRATION (in g/ml)	ABSORBANCE (at $_{MAX}$= 322 nm)
1	2	0.1174 0.0010
2	4	0.2406 0.0066
3	6	0.3639 0.0030
4	8	0.4650 0.0041
5	10	0.5767 0.0026
6	12	0.7118 0.0084

7	14	0.8192 0.0106
8	16	0.9308 0.0032
9	18	1.0520 0.0118
10	20	1.1665 0.0026

Table 1: Calibration Curve of Ketorolac Tromethamine at pH 6.8



A **B**

Figure 1: Absorption Maxima of Ketorolac Tromethamine (A) Calibration Curve of Ketorolac Tromethamine in phosphate buffer 6.8 pH (B)

FT-IR Spectroscopy

This analysis was performed to determine the functional groups consisting of TMC. The FTIR spectra of Chitosan and TMC were represented in Figure 3. The IR spectra of TMC shows peaks in the range of 1630-1660 cm^{-1} which is assigned to the quaternary ammonium salt, and peaks between 1460-1480 cm^{-1} is due to asymmetric angular deformation of CH bonds of methyl group, peak between 1415-1370 cm^{-1} is attributed to characteristic absorption of NCH_3. The examination of spectra shows that all the characteristic peaks are present in TMC and some more peaks were observed which attributed to the presence of chitosan basic structure.

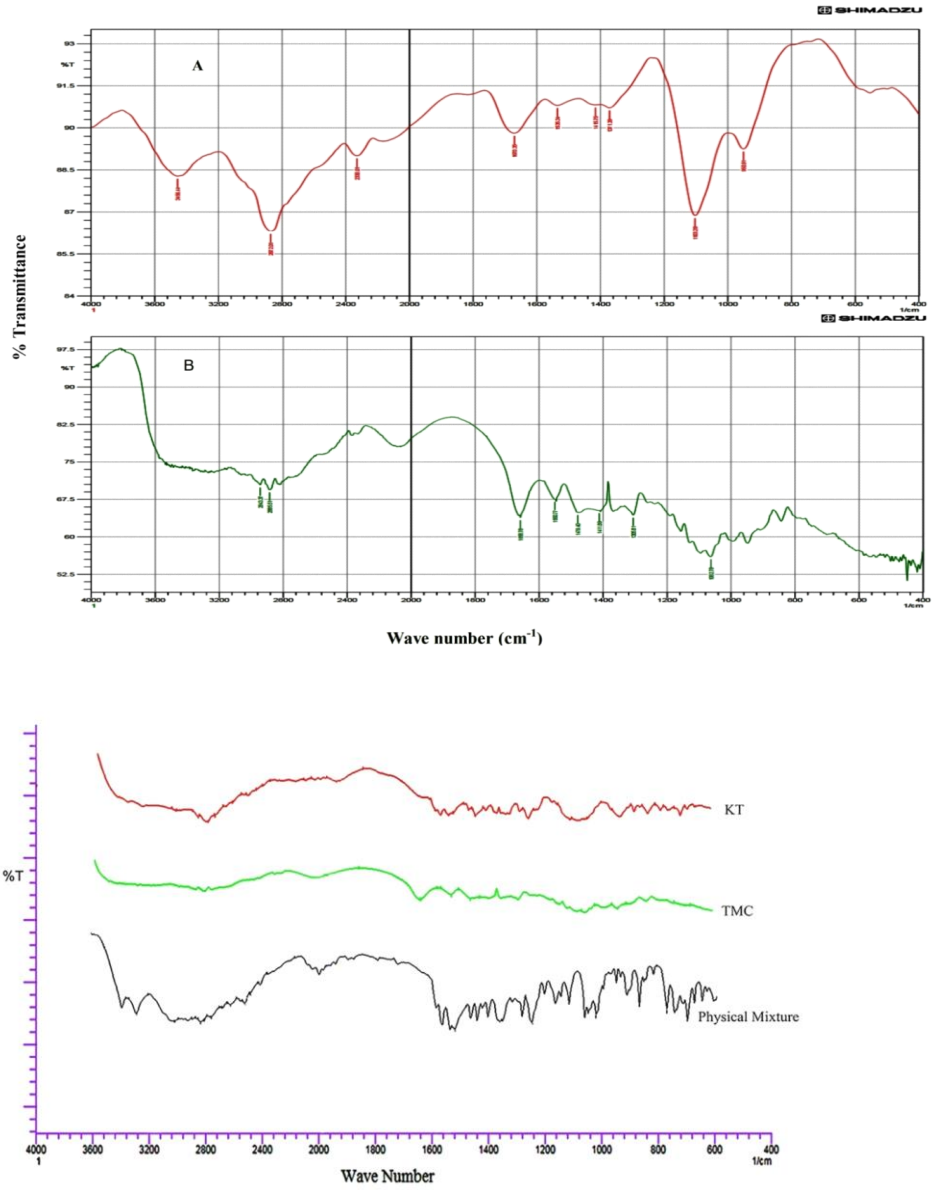


Figure 2: FTIR Spectra of Chitosan (A) and TMC (B) with Absorption Values for Functional Group and Its Peak Characteristics (C) Study of compatibility using FTIR Spectra of KT, TMC and Physical mixture.

Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR)

The NMR spectra of TMC shows a peak at 2.1 ppm attributed to hydrogen atoms of the methyl group in the acetamido group and a peak at 2.85 ppm for N, N-dimethylated group. The evidence for the appearance of N-trimethyl amino group is perceived in spectra at 3.3 ppm. The spectrum additionally shows two signals in the region of 3.38–3.51 ppm attributing to O-methylated sites. The DQ of the TMC calculated utilizing the integral of the trimethyl amino group peak at 3.3 ppm and the integral of the 1H peaks between 4.7 and 5.7 was 37.03%.

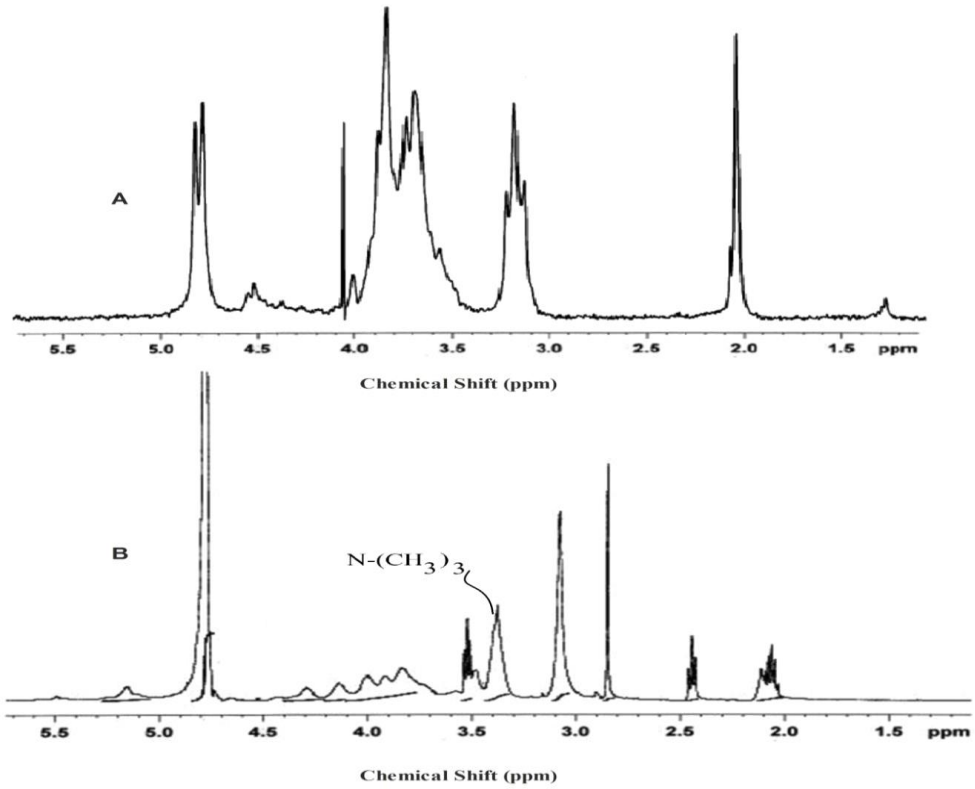


Figure 3: 1H NMR Spectra of Chitosan (A) and TMC (B) with Characteristic Chemical Shifts

Differential Scanning Calorimetry (DSC) Study

The DSC analysis of pure drug, polymer and their physical mixture were shown in Figure 4. The TMC has shown endothermic peaks at 71.30C and 202.42C. The KT has shown an endothermic peak at 168.96C with sharp crystalline integrity that associated with melting temperature (as shown by Rao et al., 2014). However, this peak was observed in physical mixture at 166.81C as shifted blunt curve due to presence of polymer **[39]**

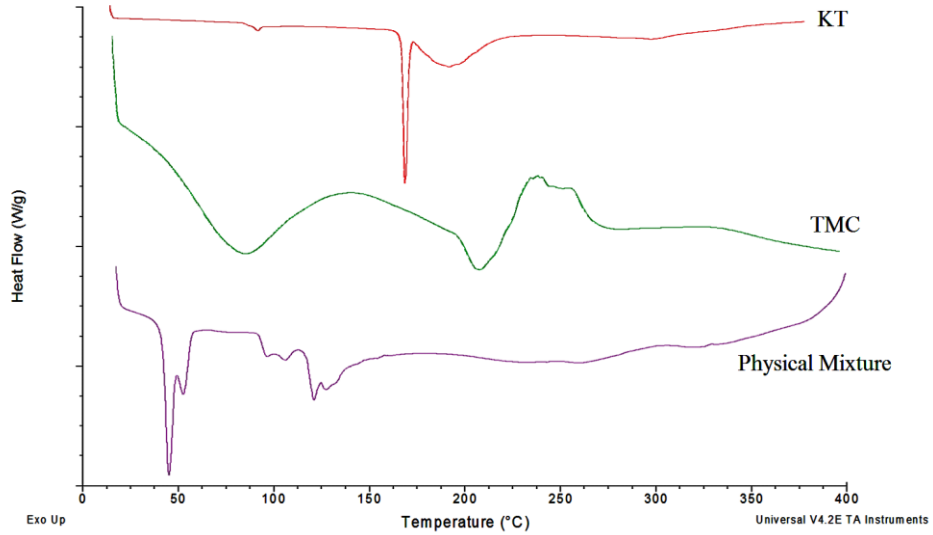


Figure 4: Study of compatibility using DSC of KT, TMC and Physical mix.

X-ray diffraction (XRD) Study

The powdered sample of ketorolac has shown characteristic intense peaks between the 2θ of 10o and 40o due to its crystalline nature. Whereas, in case formulation, no intense peaks related to drug were noticed. However, a peak at 20o observed in formulation may be attributed to the polymer crystallinity/noise. This indicates the amorphous dispersion of the drug into polymeric drop.

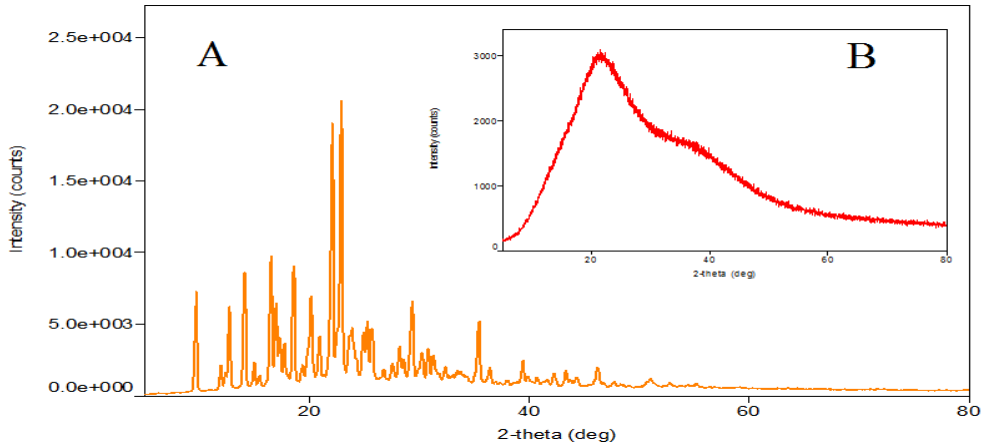


Figure 5: Study of compatibility using XRD of KT (A) and formulation (B)

Ex Vivo Permeation Studies

The present study has uncovered that TMC has enhanced the penetration capacity of formulation. It was found that the optimized formulation tested for permeation showed better drug permeation of 94.70 % in 30 min. The percentage amount of drug permeated was plotted against time to obtain permeation profile.

Figure 6: In Vitro Permeation Study Graph between Cumulative Drugs Permeated Vs. Time (Mean SD; n = 3)

In Vivo Pharmacodynamic Studies

Acetic acid is believed to act indirectly by inducing the release of prostaglandins as well as lipooxygenase products into the peritoneum which stimulate the nociceptive neurons sensitive to the non-steroidal anti inflammatory drugs hence the test is useful for the evaluation of mild analgesic non steroidal anti-inflammatory compounds.

Group	Treatment	No. of Writhes in 30 min.	Inhibition (%)
Sham Control Group	No treatment	-	-
Disease control	Simple Buffer	71.66 ± 4.13	-

Standard control	Marketed Product	34.16 ± 4.99***	52.32
Test Group I	Aq. Solution of Ketorolac	60.33 ± 7.00**	15.81
Test Group II	TMC Polymeric Drops	25.83 ± 5.19***	63.95

Values are expressed as mean S.D. n = 6 in each *P<0.05; **P<0.01; ***P<0.001 when compare to Disease control group, One way ANOVA followed by Dunnett's test

Table 2: Analgesic Activity by Acetic Acid Induced Writhing Rats

Group	Reaction Time in Seconds After Each Time Interval of				
	0 min	30 min	60 min	90 min	120 min
Sham Control	-	-	-	-	-
Disease control	2.97 ± 0.28	2.98 ± 0.39	3.00 ± 0.24	2.93 ± 0.24	3.08 ± 0.30
Standard control	2.98 0.30	5.64 ± 0.90	8.02 ± 0.26	7.75 ± 0.37	7.34 ± 0.37
Test Group I	2.98 ± 0.26	3.59 ± 0.51	3.44 ± 0.51	3.40 ± 0.40	3.35 ± 0.39
Test Group II	2.98 ± 0.24	8.97 ± 0.22	9.17 ± 0.30	8.09 ± 0.31	8.07 ± 0.29

Table 3: Analgesic Activity by Tail immersion test on Rats

Figure 8: Tail immersion Test for

Analgesic activity

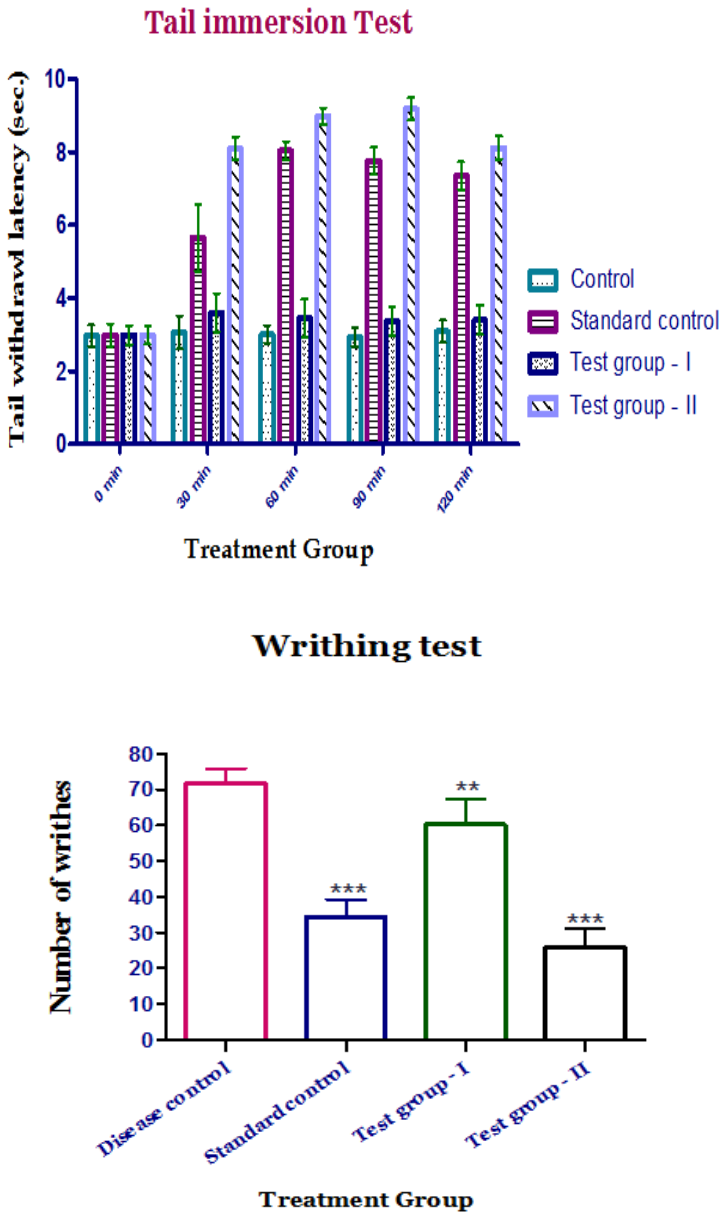


Figure 7: Acetic acid induced writhing Test for Analgesic activity

Stability Study

The result shows slight changes in the formulation property on storage. Stability testing of optimized formulation was carried out for 30 days. There was slight acceptable changes were observed in mentioned properties. The tromethamine salt form of ketorolac is found to be the most susceptible to degradation at elevated temperatures and humidity hence in accelerated stability condition it proved to be unstable and slight change in color and pH was observed.

Duration (Week)	Appearance	pH	Viscosity	% drug content	Taste
0	Opaque	5.48 ± 0.01	23.56 ± 0.12	98.74 ± 0.15	NB
1	Opaque	5.46 ± 0.05	23.71 ± 0.02	96.95 ± 1.24	NB
2	Opaque	5.50 ± 0.01	24.15 ± 0.06	96.99 ± 1.13	NB
3	Opaque	5.48 ± 0.02	24.16 ± 0.05	98.03 ± 1.30	NB
4	Opaque	5.46 ± 0.05	23.84 **±** 0.35	98.74 ± 0.45	NB

Table 6: Stability Study of Optimized Formulation (F15) Carried Out at 25 ± 2°C/ 60 ± 5 % RH

Duration (Week)	Appearance	pH	Viscosity	% drug content	Taste
0	Opaque	5.61 ± 0.05	23.56 ± 0.08	98.14 ± 0.50	NB
1	Opaque	5.71 ± 0.04	24.71 ± 0.02	97.33 ± 1.68	NB
2	Opaque	5.72 ± 0.04	24.84 ± 0.04	98.99 ± 0.17	NB
3	Opaque	5.87 ± 0.06	25.16 ± 0.05	98.85 ± 0.41	NB
4	Opaque	5.82 ± 0.04	24.85 **±** 0.06	98.74 ± 0.59	NB

All values are expressed as mean ± standard deviation, n=3; NB = Non Bitter

Table 7: Stability Study of Optimized Formulation (F15) Carried Out at 40 ± 2°C/ 75 ± 5 % RH

CONCLUSION

Ketorolac tromethamine is a potent analgesic and a moderately effective anti-inflammatory drug. It has also been used for relief of acute renal colic pain associated with trauma and visceral pain associated with cancer. The most common side effects associated with short-term administration of ketorolac tromethamine are gastrointestinal effects similar to those seen with other prostaglandin inhibitors. Ketorolac tromethamine therapy should always be initiated with IV or IM dosing and Ketorolac tromethamine Tablets USP are to be used only as continuation in the management of moderate to severe pain. The gastric irritation, bleeding, abdominal pain, heartburn and enzymatic degradation are the most common adverse effect of NSAIDs while taking orally.

Our present research work came up with an approach of overcoming the problems with oral tablet of ketorolac along with improving palatability and bioavailability compare to parenteral.

For determination of partitioning ability between aqueous and octanol phase shaking flask method was adopted which shows that KT is having good partitioning behaviour between lipid and aqueous phase with 0.29829 value.

Trimethyl Chitosan Chloride (TMC) has been shown to considerably increase the permeation of neutral and cationic peptide analogs across Caco-2 intestinal epithelia.

The viscosity and pH was observed using Brookfield and digital pH meter that shows satisfactory result (Viscosity = 23.66 ± 0.57 and pH = 5.46 ± 0.266). The viscosity ensures the flowability of formulation for administration in sublingual cavity whereas the desired pH was found to be good enough for drug as well as for the route. The drug content uniformity shows that 98.78 % drug is present in formulation. Drug excipient interaction study was observed by adopting various methods. The drug excipient interaction study via FTIR spectra shows all the characteristic peaks of drug in the physical mixture of drug along with polymers and all other excipients. The Ketorolac alone and in the form of physical mixture with polymer and excipients was also analysed for DSC thermogram. The Ketorolac alone has shown a sharp endothermic peak at 168.96 C due to melting of the drug. However, in the formulation this peak is observed as shifted blunt curve at 166.81 C due to the present of excipients and polymer, indicating the stability of drug in the formulation.

The x-ray diffraction studies are useful to investigate the solid state nature of the drugs after formulation into the dosage forms. The X-ray diffractograms of Ketorolac alone and in formulation were investigated. The powdered sample of ketorolac has shown characteristic intense peaks due to its crystalline nature.

Invitro permeation study, it was found that the optimized formulation tested for permeation showed better drug permeation of 94.70 % in 30 min.

The current study highlights the development and characterization of a TMC polymeric drops formulation of ketorolac for sublingual delivery, can be expected to result an improved drug delivery solubility of drug to avoid first-pass metabolism and bioavailability for quick management of pain.

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