ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

Formulation, Development, Evaluation and Comparative Study of Ketorolac Tromethamine Loaded Colloidal Gel

Received: 13 February 2023, **Revised:** 16 March 2023, **Accepted:** 20 April 2023

Ravindra Kumar Yadav, Preeti Gupta, Manoj Kumar Mishra*
Shambhunath Institute of Pharmacy, Jhalwa, Prayagraj-211012 (U.P.) India.

***Corresponding Author: Manoj Kumar Mishra,**
Shambhunath Institute of Pharmacy, Jhalwa, Prayagraj-211012 (U.P.) India.; bmanojmishra@gmail.com

Keywords:
Gel, Ketorolac tromethamine, Pre-formulation study, evaluation of gel.

Abstract

The aim of this study is formulation development of ketorolac tromethamine loaded colloidal gel, to evaluate pre-formulation and post-formulation parameters of gel with effect of different gelling agent and their comparative study. Initially, pre-formulation studies were done after that formulation of ketorolac tromethamine was prepared using solvent dispersion method, and then post formulation studies were done. The API used ketorolac tromethamine has excellent NSAIDs potency, which is used in formulation of gel. The gel will provide a better retention time at the site of application as well as site of drug absorption, so that the drug will get enough time for absorption. The formulation prepared will produce oral pain relief effect in case of dental problems. The various parameters studies in the formulation of gel includes: Organoleptic properties, viscosity study, in-vitro drug release study, FT-IR of API, and gelling agent. Formulation F4 provides better gelling strength to the gel with good retention\on time.

1. Introduction

For many decades, a chronic illness or an acute disease mainly controlled by drug deliveryviavarieties of pharmaceutical formulation, which includes tablet, liquid dosage form, cream, capsules, aerosol, suppositories, and parenteral as drug carrier(1,2). Indifferent routefor delivery of drug, oral route is considered as the most common route diseased individuals. The blood that drains into GIT take drug to the liver which leads to first pass metabolism with poor bioavailability(3,4).

Conventionally used drug for a treatment of oral problems like dental carries, dental pain gives lighter therapeutic response along with large amount of dose required for the treatment, which passes through a long ADME process(5,6). In order to reduce various metabolic process gel therapy will be better helpful which will provide better time of retention at site of action for treatment of disease(7,8).

The drug ketorolac tromethamine used in the formulation of gel provides better activity and its potency is 600 times the potency as the potency of aspirin(9), so its effect to lower the pain and inflammation will be very much effective because the required quantity of drug in very low quantity(10,11) with bioavailability of 80-100%(12). As per Indian Pharmacopoeia 10mg/gm of formulation is sufficient quantity to reduce the effect of pain(13,14). Ketorolac tromethamine absorbs rapidly following oral as well as intra muscular route(15,16).

The problems related to drug formulations, might resolved by modifying the route of administration or can also be by improving the formulation. Mucosal route, injectables, as well as transdermal route avoid first pass metabolism also offer other routes for systemic delivery of drugs(17). Hence oral route of administration of drug was preferably to reduce the pain of oral dental problems(18). With the formulation of colloidal gel, it will be easy for drug retention at the site of pain and inflammation(19).

The polymer Carbapol 940 is a synthetic gelling agent used to enhance the thickness of the gels, lotions as well as creams(20,21). Majorly it stabilizes the formulation, and improves controlled release of pharmaceutical as well as cosmetic products(22,23).

2. Material and Method

2.1. PRE-FORMULATION STUDY

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

2.1.1. Solubility of ketorolac tromethamine - Different solvents (Purified water, DMSO, ethanol, chloroform) is use for the determination of solubility of ketorolac tromethamine.

2.1.2. Melting Point–By using capillary tube method, melting point of Ketorolac Tromethamine was measured. In capillary tube the sample was put into it, further the sample was reserved with liquid paraffin. The apparatus temperature was raised by 0.50°C/min. after the melting of sample reading was recorded till the full sample was melted.

2.1.3. UV spectrometry - In range of 200-400 nm means UV wavelength region light absorb by most of drugs, because of aromatic structure and double bonds presence. On electronic balance weighed Ketorolac Tromethamine 100 mg quantity was and in phosphate buffer (100ml) of pH 6.8 dissolved gives1000µg/ml concentration. Ketorolac Tromethamine solubilizes in water. To gives 10 µg per ml concentration, diluted this solution with 1 ml pH 6.8 phosphate buffer (100ml) in separate container and observed under Ultra Violet spectrophotometer (visible) within 200-400 nm.

2.1.4. Fourier Transform Infra-red Spectroscopy (FTIR)

In hot air oven at 105°C,KBr was dried for 1 to 2 hours. By using pestleand mortar approximately around 600mg of potassium bromide was triturated. Around 50mg of ketorolac tromethamines was added into it further triturated. FTIR range of 4000-400 cm-1 is use for sample scanning.

2.2. Calibration curve of ketorolac tromethamine

2.2.1. 6.8 pH Phosphate buffer – In volumetric flask of 200 ml to 0.2 M Potassium dihydrogen phosphate (50 ml) a 0.2 M NaOH (22.4 ml) was added after that made up the volume up to 200ml with water(as per Indian Pharmacopoeia).

2.2.2. Preparation of ketorolac tromethamine standard curve using phosphate buffer solution 6.8-pH

- Ketorolac tromethamine drug 100 mg was dissolved in phosphate buffer of 6.8 pH small amount further100 ml volume was make up using same phosphate buffer6.8 pH which is called as stock-I solution.
- In another volumetric flask above prepared 10 ml of the solution (stock-I solution) is dilute up to 100 ml using Phosphate buffer 6.8 pH which has been known by name means Stock-II solution. By pipetting out 1ml, 2ml, 4ml, 6ml, 8ml, and 10ml serial dilutions from the stock-II solution were made to examine drug solution in between concentration from 10µg per ml, 20µg per ml, 40µg per ml, 60µg per ml, 80µg per ml, 100 µg per ml. At 323 nm solutions absorbance by UV Visible spectrophotometer was measured. A graph was plotted between Concentration Vs Absorbance.

2.3. Drug Excipients Compatibility - A small quantity of drug was transfered to 10ml of flask. Excipients were added into it and put it into a glass container. The container was closed followed by sealing. With the help of aluminium foils, sealed the container and mixed physically with excipients by 1:1 ratio. The sample was stored in a 25°C±2°C with 60% RH ±5%RH and 40°C ±2°C /75% RH ±5%RH for 14days. The sample is observed for 14 days by physical examination.

2.4. Formulation and Development

2.4.1. Solvent Selection- Different solvents were used to determine the solubility of ketorolac tromethamine. A small quantity of drug was taken and dissolved with help of magnetic stirrer. Further an access amount of drug was used and mixed well. Then filtration process is taken to remove the undissolved drug.

2.4.2. Gel phase selection-For the formulating the colloidal gel, formulation gel phase is use as a base. For the selection of gel base viscosity and site of application is the primary criteria. Gel phase is based on polymer type and it was depending on water and solvents. The rigidity of the gel based is depends on liquid entrapments.

2.5. Preparation of Colloidal Gel

- Weighed accurately (1.00% w/v, 2.00% w/v, 3.00%w/v, and 4.00%w/v) specific quantity of Carbapol 940 and Xanthem Gum.A beaker was taken to which sufficient amount of purified water was added to dissolve the polymer, Carbapol 940 and Xanthem Gumwas added slowly (so as particle agglomeration can be

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

prevented) into beaker with water. Further mixing was done completely using homogenizer at250 round per minute. To prevent bubbles in the formulation, carer must be taken. Mixing has been done to achieve homogeneous mixture. Then make up the volume with distilled water and mixed well.

- Then at the endphase of mixing, remaining excipients were added followed by addition of ketorolac tromethamine.

Table 1: Description of Formulations Prepared

Each 5gm of formulated gel contains									
S.No.	**Formulation code**	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**
1.	Ketorolac Tromethamine	50	50	50	50	50	50	50	50
2.	Carbapol 940	50	100	150	200	-	-	-	-
3.	Xanthen Gum	-	-	-	-	50	100	150	200
5.	Propylene glycol	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
4.	Liquid Paraffin	1.0ml	1.0ml	1.0ml	1.0ml	1.0ml	1.0ml	1.0ml	1.0ml
6.	Methyl Paraben	0.4 ml	0.4 ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
7.	Agar	100	100	100	10	10	10	10	100
8.	Mint	0.1 ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml
9.	Purified Water	q.s	q.s	q.	q.s	q.s	q.s	q.s	q.s

3. Evaluation

3.1. Physical Appearance: Prepared colloidal gel was visually inspected. The formulation was observed for their appearance, colour, consistency, grittiness, homogeneity.

3.2. Melting Point: The melting point of ketorolac tromethamine was calculated with the help of Macro Scientific Works melting point apparatus.

3.3. In-vitro Release: In-vitro drug release study was done with the help of USP type 1 apparatus (basket), themedium of dissolution maintained is phosphate buffer having pH 6.8. The temperature of the dissolving medium was maintained up to 37±2°C forrpm of 50. Withdrawn 1ml sample was at various interval of time, and at the same time sample replaced with equal volume of phosphate buffer so sink condition will be maintained. The samples was analysed byspectrophotometreat323nm for **ketorolac tromethamine**,and the percent drug releasedwascalculated.

4. Result & Discussion

4.1. Physical Appearance - Organoleptic properties of Ketorolac Tromethamine were observed and their result shown in table –

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Table 2: Description of pure Ketorolac Tromethamine

Properties	**Observation**	**Reference**
Colour	White to light yellow powder	White to light yellow powder
Physicalnature	Solid	Solid
Odour	Unpleasant	Unpleasant

4.2. Solubility – The drug was found to be soluble in Purified water, DMSO and Ethanol as per certificate of analysis and experimental data.

4.3. Physical Examination: The formulations of Colloidal gel were yellowish white viscous cream like formulation having glossy appearance and even homogenous mixture.

Table 3: Description of Formulations

Formulations	**Colour**	**Homogenesity**	**Consistency**
F-1	White	Fair	Excellent
F-2	White	Excellent	Excellent
F-3	White	Excellent	Very Good
F-4	White	Excellent	Excellent
F-5	Yellowish White	Excellent	Poor
F-6	White	Fair	Excellent
F-7	Light Yellow	Excellent	Fair
F-8	White	Excellent	Excellent

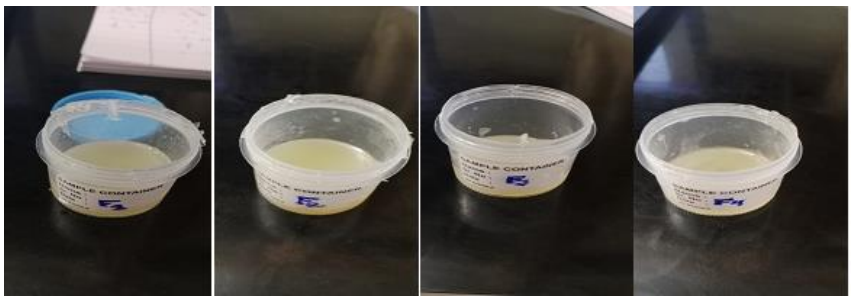

Figure 1: Showing Formulation of different concentration of carbapol 940

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Fig 2: Figure Showing Formulation of different concentration of Xanthem Gum

4.4. Melting Point determination

Table 4: Melting point analysis of Ketorolac Tromethamine is shown in the table

Properties	Observed value	Melting point ranges
Ketorolac Tromethamine	162-165°C	163°C

4.5. UV Spectroscopy of ketorolac tromethamine- The UV spectroscopy of gel was done using UV Spectrophotometer and the peak spectra was obtained at 323nm.

4.6. FTIR Spectroscopy of ketorolac tromethamine

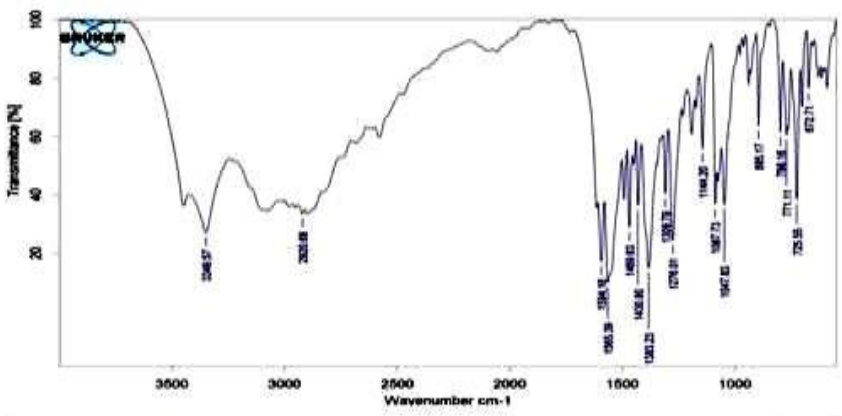

Figure 3: Figure showing FTIR of ketorolac tromethamine

5. Summary and Conclusions

This study shows the formulation development, evaluation studies and comparative study of the effect of various gelling agent on ketorolac tromethamine loaded colloidal gel. Drug ketorolac tromethamine was selected to study. Ketotolac tromethamine isa (NSAID) nonsteroidal anti-inflammatory drug. This drug generally used to treat inflammation, to overcome swelling, as well as joint pain related. Solubility of drug was examined in DMSO, Purified water, DMF. The melting point of drug obtained at163°C. Physical appearance in F4 formulation obtained excellent and show good result for further studies. Bio-adhesive strength and spreadibility of formulation F3 and F4 containing the polymer Carbapol 940 was found to be Excellent. The compatibility studies were done using FTIR in which drug polymer compatibility was examined and no physicochemical interaction found. In this project,

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Carbapol 940 has excellent gelling property for formulation Ketorolac Tromethamine loaded colloidal gel.

FUNDING

Nil

CONFLICT OF INTEREST

None

References

[1] Okur NÜ, Bülbül EÖ, Yağcılar AP, Siafaka PI. Current Status of Mucoadhesive Gel Systems for Buccal Drug Delivery. Curr Pharm Des. 2021 May;27(17):2015–25.

[2] Bannigan P, Aldeghi M, Bao Z, Häse F, Aspuru-Guzik A, Allen C. Machine learning directed drug formulation development. Adv Drug Deliv Rev. 2021 Aug; 175:113806.

[3] Jain KK. An Overview of Drug Delivery Systems. In 2020. p. 1–54.

[4] Kienzler JL, Gold M, Nollevaux F. Systemic Bioavailability of Topical Diclofenac Sodium Gel 1% Versus Oral Diclofenac Sodium in Healthy Volunteers. The Journal of Clinical Pharmacology. 2010 Jan;50(1):50–61.

[5] Swami R, Shahiwala A. Impact of physiochemical properties on pharmacokinetics of protein therapeutics. Eur J Drug MetabPharmacokinet. 2013 Dec 14;38(4):231–9.

[6] Tang D, Chen K, Huang L, Li J. Pharmacokinetic properties and drug interactions of apigenin, a natural flavone. Expert Opin Drug MetabToxicol. 2017 Mar 4;13(3):323–30.

[7] Whitaker KA, Varga Z, Hsiao LC, Solomon MJ, Swan JW, Furst EM. Colloidal gel elasticity arises from the packing of locally glassy clusters. Nat Commun [Internet]. 2019;10(1). Available from: http://dx.doi.org/10.1038/s41467-019-10039-w

[8] Woll KA, Schuchardt EJ, Willis CR, Ortengren CD, Hendricks N, Johnson M, et al. Gel Formulation Containing Mixed Surfactant and Lipids Associating with Carboplatin. Chem Biodivers. 2011 Dec;8(12):2195–210.

[9] Vadivelu N, Gowda AM, Urman RD, Jolly S, Kodumudi V, Maria M, et al. Ketorolac tromethamine - Routes and clinical implications. Vol. 15, Pain Practice. Blackwell Publishing Inc.; 2015. p. 175–93.

[10] Gujarathi, N. A., Rane, B. R., & Keservani, R. K. (2017). Liquid Crystalline System: A Novel Approach in Drug Delivery. In Novel Approaches for Drug Delivery (pp. 190-216).

[11] Behera, J., Keservani, R. K., Yadav, A., Tripathi, M., & Chadoker, A. (2010). Methoxsalen loaded chitosan coated microemulsion for effective treatment of psoriasis. International Journal of Drug Delivery, 2(2).

[12] Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. Eur J Clin Pharmacol. 1988;35(4):423–5.

[13] Buckley MMT, Brogden RN. Ketorolac. Drugs [Internet]. 1990;39(1):86–109. Available from: https://doi.org/10.2165/00003495-199039010-00008

[14] Vadivelu N, Gowda AM, Urman RD, Jolly S, Kodumudi V, Maria M, et al. Ketorolac tromethamine - Routes and clinical implications. Pain Practice. 2015;15(2):175–93.

[15] Joishy SK, Walsh D. The Opioid-Sparing Effects of Intravenous Ketorolac as an Adjuvant Analgesic in Cancer Pain. J Pain Symptom Manage. 1998 Nov;16(5):334–9.

[16] Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. Eur J Clin Pharmacol. 1988;35(4):423–5.

[17] El Moussaoui S, Abo-Horan I, Halbaut L, Alonso C, Coderch L, Garduño-Ramírez ML, et al. Polymeric Nanoparticles and Chitosan Gel Loading Ketorolac Tromethamine to Alleviate Pain Associated with Condyloma Acuminata during the Pre- and Post-Ablation. Pharmaceutics. 2021 Oct 25;13(11):1784.

[18] Keservani, R. K., Bandopadhyay, S., Bandyopadhyay, N., & Sharma, A. K. (2020a). Design and fabrication of transdermal/skin drug-delivery system. In Drug Delivery Systems (pp. 131-178). Academic Press.

[19] Lu PJ, Weitz DA. Colloidal particles: Crystals, glasses, and gels. Annu Rev Condens Matter Phys. 2013 Apr;4(1):217–33.

[20] Bonete JM, Tamashiro JR, Paiva FFG de, Queiroz-Fernandes GM de, Guidelli É, Baffa O,

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

et al. Influence of silver nanoparticles on the tissue reaction of polyacrylic acid-based gel. Acta Cir Bras. 2022;37(5).

[21] Ay Şenyiğit Z, Coşkunmeriç N, Çağlar EŞ, Öztürk İ, AtlıhanGündoğdu E, Siafaka PI, et al. Chitosan-bovine serum albumin-Carbopol 940 nanogels for mupirocin dermal delivery: ex-vivo permeation and evaluation of cellular binding capacity via radiolabeling. Pharm Dev Technol. 2021 Sep 14;26(8):852–66.

[22] Mallawarachchi S, Mahadevan A, Gejji V, Fernando S. Mechanics of controlled release of insulin entrapped in polyacrylic acid gels via variable electrical stimuli. Drug Deliv Transl Res. 2019 Aug 14;9(4):783–94.

[23] Hägerström H. Polymer gels as pharmaceutical dosage forms [Internet]. Acta Universitatis Upsaliensis. 2003. Available from: http://uu.diva-portal.org/smash/get/diva2:163176/FULLTEXT01.pdf