ISSN 2582-6441 [Online]
RESEARCH JOURNAL OF PHARMACY AND LIFE SCIENCES
LET OTHERS KNOW YOUR RESEARCH
RJPLS
An International Peer Reviewed Journal

Research Article

EXTRACTION, FORMULATION AND EVALUATION OF THERMO-REVERSIBLE ORAL GEL OF CURCUMIN FOR MOUTH ULCERS

Asish Sahu*, Anjan Kumar Mahapatra, Ajit Kumar Acharya

Royal College of Pharmacy and Health Sciences, Berhampur, 760002, Odisha, India

ARTICLE INFO

Date of submission: 18-05-2024
Date of Revision: 02-06-2024
Date of acceptance: 09-07-2024

Key Words:
Sol-Gel transfer, thermo reversible gel, mouth ulcer, bioadhesion, sustained release.

ABSTRACT

Curcumin is used for its various therapeutically effectiveness for many diseases from ancient times. Among all the diseases in oral cavity mouth ulcer is found to be the most common one, For the treatment of mouth ulcer, number of dosage forms are available in the form of suspension, ointment etc. Now days the one dosage form that is proved to be more effective than the conventional dosage liquid forms is the Sol-Gel transfer. The current experiment was carried to prepare Thermo reversible gel containing curcumin for the treatment of mouth ulcer. In the formulation hydroxy propyl methyl cellulose (HPMC) was taken as the thermo reversible agents in combination with carbomers as the bioadhesive polymers. From IR and DSC Studies it was found that curcumin is compatible with all excipients used in the formulation and the studies shows no significant interaction among the drug and excipients. Six different formulations were made by taking different concentrations. The formulations were verified for gelation temperature, pH, gel strength and in vitro drug release. It was observed that increase in the concentration of bioadhesive agent enhanced the bioadhesive force significantly. Both the batches were found to be satisfactory. The formulations delivered drug for about 4 h. It was observed from the results that the residence time as well as the contact area of curcumin at the ulcer can be enhanced along with a sustained release. It can be concluded that thermo reversible gel of curcumin can be ideal candidate for mouth ulcer.

***Corresponding author:**

Mr. Asish Sahu

Asst. Professor, Department of Pharmaceutics

Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India.

Tel: +91-9337572847, E-mail address: asishsahu24@gmail.com

INTRODUCTION

The oral cavity, or more commonly known as the mouth or buccal cavity, serves as the first portion of the digestive system. Mouth ulcers also known as canker sores are normally small, painful lesions that develop in mouth or at the base of your gums. A mouth ulcer (aphtha) is an ulcer that occurs on the mucous membrane of the oral cavity [1]. Common causes of mouth ulcers include nutritional deficiencies such as iron, vitamins, especially B_{12} and C, poor oral hygiene, infections, stress, indigestion, mechanical injury, food allergies, hormonal imbalance, skin disease etc. [2]. Mucoadhesion, an interfacial phenomenon, is based on two materials, one of which is mucus layer of mucosal tissue to which the drug is held together by means of interfacial forces for prolonged period of time. Control release system ensures localization of drug in a particular site to improve and increase the bioavailability. The contact time is also enhanced due to interaction between polymers and mucus lining of tissue for sustained action [3].

Curcumin is extracted from curcuma longa, a type of herbal compound originating from the ginger family (Zingiberaceae) [4]. Rhizomes are horizontal underground stems that send out shoots as well as roots. The bright yellow colour of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids. Curcumin is a bright yellow chemical produced by plants of the curcuma longa species. It is the principal curcuminoid of turmeric. It is sold as an herbal supplement, cosmetics ingredient, food flavouring, and food colouring [5]. It is used in topical applications to treat conditions like eczema and psoriasis due to its anti-inflammatory and antimicrobial properties [6]. Curcumin may help protect against heart disease may help prevent (and possibly treat) certain types of cancer, may help ease symptoms of osteoarthritis. May help delay or reverse Alzheimer's disease [7, 8].

Over the past five decades, curcumin has undergone extensive research, which showed it as a potent pharmacological molecule with a broad spectrum of biological activities proven in vitro [9]. The oral cavity is the target for localised release of curcumin which presents an opportunity to optimize its affect by avoiding the intestinal and first pass metabolism which may extend its residence time on the applied area [10]. The structure of curcumin is given under Figure 1.

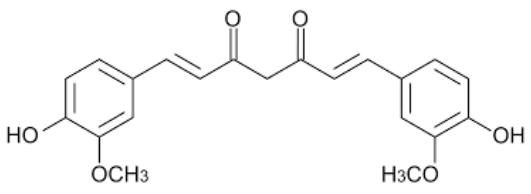

Figure 1: Structure of curcumin

The gel dosage form overcomes the disadvantages of liquid dosage form and solid dosage forms [11]. *In situ* gelling system should be a low viscous, free flowing liquid to allow for reproducible administration as drops, and the gel formed following phase transition should be strong enough to with stand the shear forces in the applied area and demonstrated long residence time. In order to increase the effectiveness of the drug a dosage form should be chosen which increases the contact time of the drug. This may then prolonged residence time of the gel formed in situ along with its ability to release drugs in sustained manner will assist in enhancing the bioavailability, reduce systemic absorption and reduce the need for frequent administration leading to improved patient compliance [12].

MATERIALS AND METHODS

Materials

Curcumin was extracted from the rhizomes of curcuma longa. HPMC was obtained from S&A chemicals, Mulund west, Mumbai. Carbopol was obtained from Dzone international, Mumbai. NaOH was purchased from E. Merck India Pvt.Ltd., Mumbai. All other chemicals were of analytical grade.

Methods

Extraction of curcumin

About 100 gm of turmeric powder was extracted with 95 % alcohol by maceration process until all the colouring matter is extracted [15]. The alcoholic extract was distilled off to a semi-solid brown coloured mass. The crude extract was dissolved in 50 mL of benzene and extracted twice with equal volume of 0.1 % sodium hydroxide solution. The alkaline extract was combined and acidified with dilute hydrochloric acid. A yellow-coloured precipitate is formed; it was allowed to settle for about fifteen minutes. After setting of precipitate, the concentrate was extract by boiling on water bath and at the same time the precipitate was dissolved in boiling water. During this process of boiling, the resinous material would agglomerate and lumpy mass was formed. The solution was filtered out in hot condition and concentrates filtrate to very small volume and cools to get curcumin (15 %). Curcumin is an orange yellow crystalline powder. For the confirmation whether the extracted product is curcumin or not the extracted powder was subjected to different tests. The extracted powder was dissolved in methanol and its absorbance was determined in UV-spectrophotometer i.e. 433 nm and its melting point is also determined which is around 182 ℃. It was insoluble in cold water, ether and soluble in alcohol and glacial acetic acid. It was dissolved in concentration sulphuric acid and gives a yellow-red coloration. In 0.1N

sodium hydroxide gives deep brown colour [16].

Linear Plot of curcumin

Curcumin (25 mg) was dissolved in 25 mL of methanol and volume was made to 100 mL with distilled water to from a clear solution. Linear plot was obtained by preparing standard solutions of curcumin ranging from 2 to 14 µg/mL. The absorbance of the solution was measured spectrophotometrically at 435 nm.

IR Spectroscopy Studies

A drug and carrier interaction study was done using IR spectroscopy (Shimadzu, Japan, FTIR-8400S). The spectra were obtained for both. Samples were made using KBr discs and scanning from 400-4000 cm^{-1}.

DSC Studies

The thermal behaviour of the drug carrier used in the inclusion complexes was studied using a differential scanning calorimeter (DSC 4000, Perkin Elmer, America). A sample of 5 mg was kept in an Al pan and sealed. The isothermal process of study was maintained 40 °C/m and a flow rate of 25 mL/ m at temp. range of (5-300 °C) in an atmosphere of N_2 as purge gas [17].

PREPARATION OF FORMULATION:

Selection of Base:

Different compositions of carbopol 934P, xanthangum, guargum and HPMC were mixed to check the compatibility and capability of forming the gel out of which the combinations of carbopol 934P and HPMC showed the desired results**.**

Preparation of Base:

Carbopol 934P was added slowly to 20 mL of distilled water with continuous stirring with a concentration of 0.7 %, 0.6 % and 0.5 % respectively until a clear solution is obtained. To this HPMC was added to solutions at 1 % and 2 % concentration.

Test sample:

To the prepared base extracted curcumin was added at 1 % concentration with continuous stirring and the volume was made up to 50 mL by adding distilled water and the solution phase is prepared. The formulation table is given in the Table-1.

Table 1: Formulation of curcumin Thermo reversible gel

Sl.No.	NAME	F1	F2	F3	F4	F5	F6
1	CURCUMIN	0.5gm	0.5gm	0.5gm	0.5gm	0.5gm	0.5gm
2	CARBOPOL	0.35gm	0.3gm	0.25gm	0.35gm	0.3gm	0.25gm
3	HPMC	0.5gm	0.5gm	0.5gm	1gm	1gm	1.gm
4	DISTILLEDWATER	Up to 50ml	Up to 50ml	Up to 50ml	Up to 50ml	Up to 50ml	Up to 50ml

EVALUATION OF FORMULATIONS [18]

Appearance

Formulations were examined visually for texture and clarity against white background and for the presence of particulate matter any if present.

pH measurement

The pH of the gel was determined using a calibrated pH meter at 4 ℃. The readings were taken for an average of 3 samples.

In vitro gelation studies

The reversible sol-gel transition temperature and time was measured by test tube tilting method (TTM). To measure the gelation temperature, the solution (10 mL) was sealed in a 10 mL glass tube and placed in controlled temperature bath. The temperature of bath was increased at a very slow rate. At a certain temperature the solution was completely converted into gel. The gel became viscid and did not flow with the tilting of the test tube. This characteristic temperature is called gelation temperature and the time noted is called gelation time. Same process has been repeated 2-3 times to get the accurate value.

Gels strength

Gel strength is important in finding the condition, which can delay the anterior leakage. Optimal *in situ* gel must have suitable gel strength so as to be administered easily and can be retained at oral mucosa without leakage after administration. The gel strength of the in-situ gels were performed by using the ball (10 mg) placed in a 100 mL beaker containing *in situ* gel and measured by time taken for ball to penetrate 5 cm.

Syringeability

The ability of the prepared formulations to flow easily through a syringe of 21-gauge needle was assessed using the reported method. One ml of the cold gel was filled in 21-gauge needle syringe and the ability of the gel to flow under normal handling pressure was assessed.

Drug content

Drug content was determined by dissolving an accurately weighed quantity of formulation (1000 mg) in 20 mL of methanol. The solutions were then further diluted with methanol and filtered through 0.45 m membrane filter and analyzed for curcumin content by UV spectrophotometer at 435 nm.

Spreadability

For the determination of spreadability, a lab-fabricated apparatus was used. The apparatus consists of a glass slides fixed on a wooden block with a pulley. Another glass slide is kept over the fixed slide and is attached with a string running over the pulley. A fixed weight is attached to the free end of the string. Sample of thermo reversible gel was applied in between two glass slides and was compressed to

uniform thickness by placing 2 g weight for 1 m. The time (t) in which the upper glass slide moves over to the lower slide upto the predefined length (L) was measured. The spreadability (S) was calculated by the formula:

S= ML/t.

***In vitro* drug release**

The *in vitro* release of the prepared formulations was studied through dialysis membrane using a Franz diffusion cell. The dialysis membrane was previously soaked overnight in dissolution medium (Phosphate buffer PH 7.4 with SLS) the dialysis membrane was placed between the donor and receptor compartment. The receptor compartment was filled with 50 mL of freshly prepared Phosphate buffer (pH 7.4). 1 mL of test formulation was placed on the donor compartment. Evaporation of the test formulation was prevented by sealing the opening of the donor compartment with a glass cover sip, while the receptor fluid was maintained at 37 ℃ with constant stirring at a 50 rpm, using a Teflon-coated magnetic stir bead. 3 mL sample was withdrawn from the receptor compartment at various time intervals up to 240 m and withdrawn sample were replaced with equal volume of the Phosphate buffer. The samples were analyzed for the curcumin by the measuring absorbance at 435 nm in a UV-spectrophotometer.

RESULTS AND DISCUSSION

Table-2: StandardCurveof Curcumin in methanol

Curcumin Concentration (ppm)	Absorbance at 435nm
0	0
2	0.313
4	0.586
6	0.919
8	1.184
10	1.514

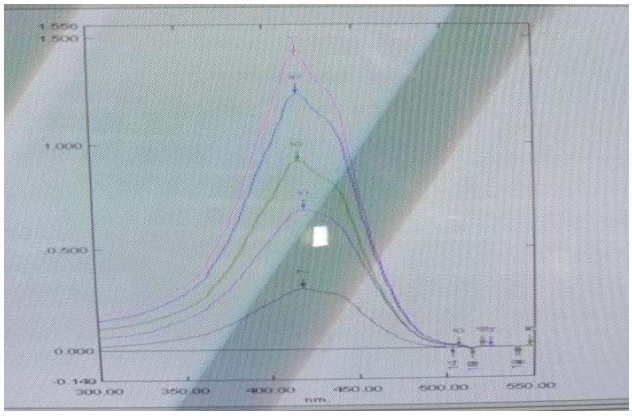

Figure 2: UV Spectrum of curcumin

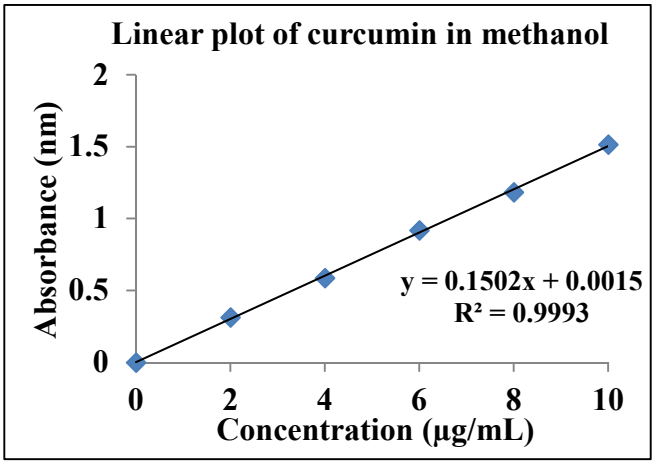

Figure 3: Linear plot of curcumin

IR spectroscopy studies

The result of the peaks observed are discussed as: in the IR spectra of curcumin the peaks at 3514.3 cm^{-1} is due to O-H stretching. 2916.37 cm^{-1} may be due to the presence of C-H bond. 1600.92 cm^{-1} is due to C=O stretching, 1510.26 cm^{-1} peaks is due to C=C stretching. Similarly, the physical mixture i.e., curcumin, HPMC and carbopol 934P shows the peaks at 3510.45 cm^{-1} is for O-H stretching and 1749.44 cm^{-1} is due to stretching of C=O group. Although some shifts in the peak was observed but still the important peaks are retained. The IR spectrum is given under **Figure 4** and **Figure 5**.

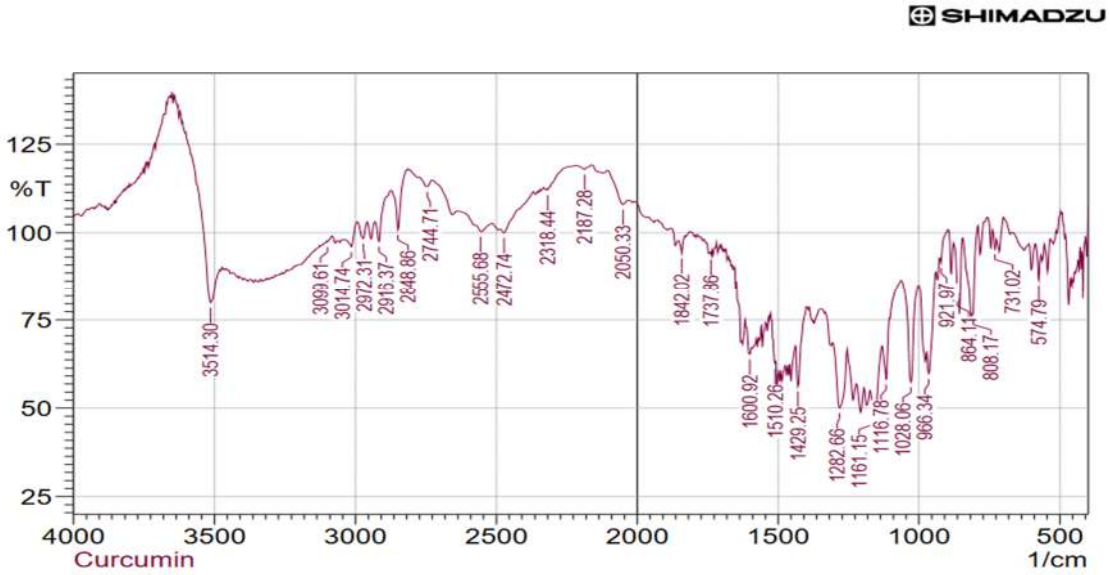

Figure 4: **FT-IR Spectra of Curcumin (pure drug)**

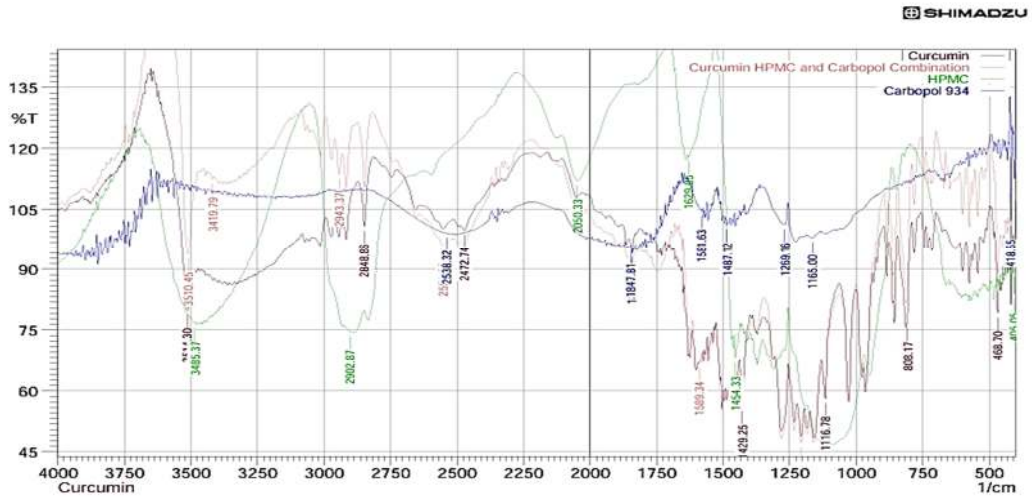

Figure 5: **FT-IR overlay Spectra of (A) Curcumin (pure drug), (B) HPMC, (C) Carbopol 934P, (D) Curcumin + HPMC + Carbopol 934P**

DSC Studies

Drug and excipients were evaluated for its compatibility through DSC thermogram analysis. The thermogram was run in range of 40 to 300 ^{0}C at a thermal rate of 20 ^{0}C/min. From the results it was observed that curcumin shows a sharp peak indicating melting point at a temperature of 182 ℃ ensuring the purity of drug. DSC studies did not reveal any notable interactions between the drug and polymers utilized in the gel formulations. The DSC thermogram was presented in **Figure 6** and **Figure 7.**

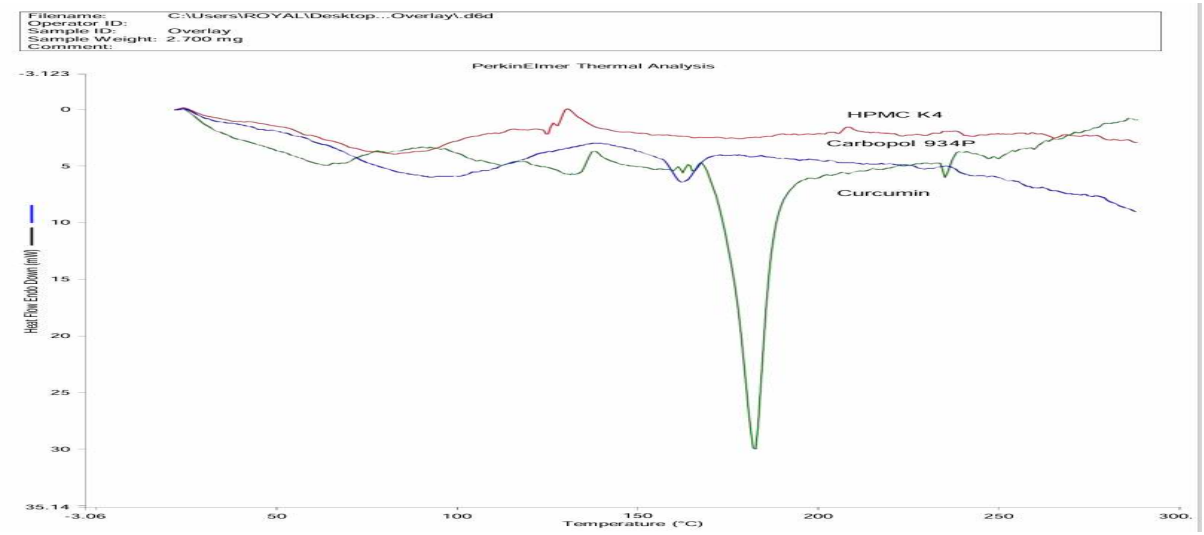

Figure 6: DSC for (A) Curcumin, (B) HPMC and (C) Carbopol 934P

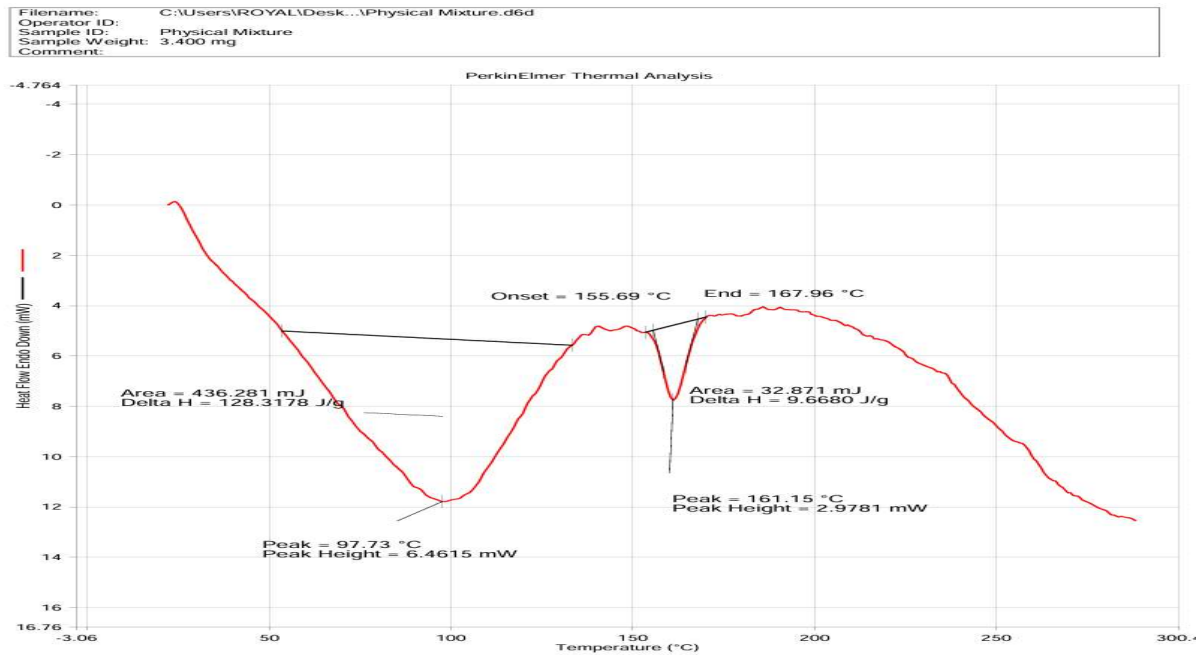

Figure 7: DSC for physical mixture of Curcumin + HPMC + Carbopol 934P

Table 3: *In vitro* evaluation of *in situ* gels

Formulation	Ph	Texture	Clarity	Gelation Temperature (°C)	Gel Strength (Sec)	Drug Content (%)	Spreadability (Sec)
F1	6.9±0.042	Sticky, non-Greasy	Clear	37±0.31	47±0.04	83.1±0.11	3.72±0.12
F2	7.1±0.05	Sticky, non-Greasy	Clear	37±0.29	44±0.09	79.7±0.17	3.64±0.23
F3	6.7±0.70	Sticky, non-Greasy	Clear	36±0.33	38±0.13	78.5±0.24	3.43±0.52
F4	7.1±0.22	Sticky, non-Greasy	Clear	37±0.15	44±1.67	81.2±0.13	4.21±0.05
F5	7.3±0.37	Sticky, non-Greasy	Clear	36±0.33	42±1.44	80.1±0.06	3.69±0.03
F6	6.7±0.34	Sticky, non-Greasy	Clear	34±0.05	40±1.07	77.3±0.16	3.52±0.19

Table 4: *In-vitro* drug release in phosphate buffer (pH7.4)

Time (min)	Cumulative % drug					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
15	6.12	6.74	9.2	4.05	6.97	7.91
30	10.77	11.64	12.31	7.12	12.61	13.45
60	15.81	19.22	26.43	11.92	20.04	22.59
90	27.77	30.54	33.96	16.53	27.56	30.73
120	34.49	39.03	44.38	23.75	35.85	40.37
150	49.56	51.18	57.47	31.21	46.17	54.82
180	52.03	60.43	65.59	42.86	52.34	62.12
210	59.49	66.32	71.54	48.47	57.21	68.04
240	64.94	71.48	80.48	57.91	65.93	75.84

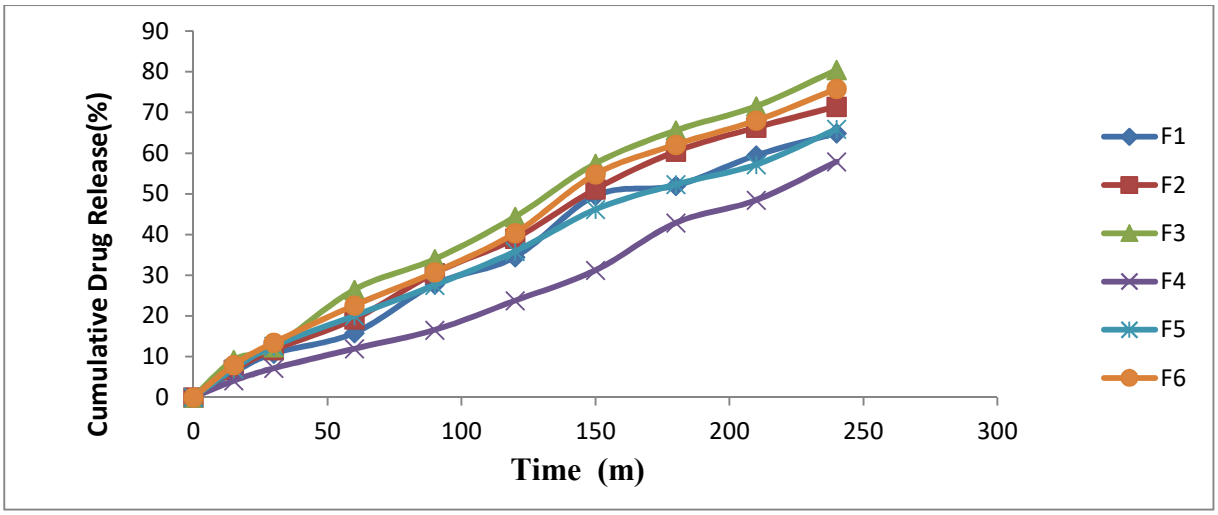

Figure 8: Comparative *In-vitro drug release* data of prepared formulations (F1-F6).

DISCUSSION

HPMC has gelation temperature around 50 ℃ but addition of NaOH might reduce the gelation temperature. The results (Table 3) showed that, the gelation temperature was 34 ℃ to 37 ± 0.5 ℃. All the formulations were sticky, non-greasy and clear. The pH of the formulations was 6.7 to 7.3. The gelling system was syringe able and passed with ease through 21-gauge needle. Gel strength was 38 to 47 sec which indicates high viscous of the gel matrix. The spreadability study showed in the range of 3.43 to 4.21 sec. Drug content of the formulations was 79.7 % and 83.12 % respectively.

In vitro drug release study (Table 4, Figure 8) shows, out of all the batches F3 and F1 shows the highest and the lowest release of drug. In 15minutes 9.2 % to 6.12% from the formulation F3 and F1 respectively. While at 240 minutes it was 80.48% & 64.94%. Which indicates F3 formulation could sustain drug release better than F1 as its gel strength was more.

CONCLUSIONS

The attempt was made to bridge the indigenous knowledge of medicine with the modern and novel drug delivery system by formulating mucoadhesive thermo reversible sol gel system of curcumin using thermo reversible polymers such as HPMC and mucoadhesive polymers such as carbopol 934P of different concentrations. The prepared formulations were shown the gelation temperature at about 36-38 ℃. All batches were found to be satisfactory results for gelation temperature, gel strength, In-*vitro* drug release etc. The formulated drug delivery system was found to be delivering the drug

over an extended period of time for about 4 h and all the formulations show a drug release of more than 50 %, while in the F3 formulations the drug release was over 80 %. Hence, it can be concluded that the *in situ* gel of curcumin is an ideal candidate for mouth ulcer. Further studies are required for the *in vivo* analysis and effectiveness of the formulations.

ACKNOWLEDGEMENT

We thank RCPHS, Berhampur for supporting to carry out the DSC and IR studies.

CONFLICT OF INTEREST

NIL

REFERENCES

1. Harris MS and Hovan AD. (2020). Oral mucosal lesions: Diagnosis and management. Journal of the American Dental Association. 2020; 151(8): 606-614.
2. Thorat YS, Sarvagod AM, Kulkarni SV and Hosmani AH. Treatment of mouth ulcer by curcumin loaded thermo reversible mucoadhesive gel: a technical note. Int J Pharm Pharm Sci, 2015; 7(10): 399-402.
3. Goswami DS and Choudhuy PK. Formulation and Evaluation of Amoxicillin Mucoadhesive Tablets. Research Journal of Pharmacy and Life Sciences. 2020; 2(2): 59-64.
4. Meybodi SM, Rezaei P, Faraji N, Jamehbozorg K, Ashna S, Shokri F, Goleij P, Moradi S, Kashian M, Arefnezhad R and Sahebkar A. Curcumin and its novel formulations for the treatment of hepatocellular carcinoma: New trends and future perspectives in cancer therapy. Journal of Functional Foods. 2023;108: 105705.
5. Kumar S and Goel A. Curcumin: A review of its effects on human health. Biological and Pharmaceutical Bulletin. 2019; 42(4): 668-674
6. Schiborr C, Zauscher J and Riedel R. Curcumin and its metabolite, tetrahydrocurcumin, reduce skin inflammation in a model of acute contact dermatitis. Journal of Dermatological Science. 2016; 83(1):39-46.
7. Panahi Y, Khalafi M and Sahebkar A. Curcumin as a potent natural therapy for osteoarthritis and rheumatoid arthritis: A review. Clinical Interventions in Aging. 2016; 11:2263-2271.
8. Mahdavi AN, Khosravi AV, and Izadpanah RM. Curcumin: A Review of Its' Effects on Human Health. Anticancer Agents in Medicinal Chemistry. 2020; 20(5): 569-586.
9. Popović VB, Farhat EK, Banjari I, Kadić AJ and Puljak L. Bioavailability of Oral Curcumin in Systematic Reviews: A Methodological Study.

Pharmaceuticals (MDPI). 2024; 17(2): 164.

10. Nasra MMA, Khiri HM, Hazzah HA and Abdallah OY. Formulation, *in vitro* characterization and clinical evaluation of curcumin *in situ* gel for treatment of periodontitis, Drug Delivery. 2017; 24(1), 133-142.
11. Gohel MC, Rajesh K. Parikh RK, Mishra S and Mohapatra A. Formulation and evaluation of oral soft gel of metformin: a patient friendly dosage form. Research Journal of Pharmacy and Life Sciences. 2020; 1(1): 22-30.
12. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm. 2002; 28(5):473-93.
13. Patil P and Patel M. Extraction and characterization of curcumin from turmeric. In Natural Products Extraction: Principles and Applications. Wiley. 2017: 143-167.
14. Teofilo V, Bruno S and Paulo C. Solid dispersions as strategy to improve oral bioavailability of poor water-soluble drugs. Drug Discovery Today. 2007; 12: 23-24.
15. Sahu A, Acharya AK and Mishra AB. Formulation and Evaluation of Celecoxib In-Situ Ophthalmic Gel. Research Journal of Pharmacy and Life Sciences. 2022; 3(1):71–78.