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Review Article

Design and Evaluation of Curcumin Plant Extract Nano Formulation as Mucoadhesive Gel

J Ramesh Babu*, J Subbarao, P Vijeta and S Vidyadhara

Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, A.P, India

***Corresponding Author:** J Ramesh Babu, Professor and H.O.D, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, A.P, India.

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Abstract

This study aimed to formulate and evaluate buccal mucoadhesive gels of native and nanosized curcumin.. Curcumin nanosuspensions were prepared using media milling technique. HPMC E15 and tween 80 were used as stabilizer and surfactant respectively. The particle size, zeta potential and PDI of formulations F1 and F3 were 193.4 and 154.9 nm, -15.1 and -18.3 mV, 0.214 and 0.229 respectively. Therefore the nanosuspension formulations F1 and F3 were selected for the further studies due to their higher stability among prepared formulations. Buccal gels with 1:1 ratio of Sodium CMC and Carbopol 934 was selected for the further drug loading. Buccal gels were then loaded with native and nanosized curcumin and were named as GF N, GF 1 and GF 3, respectively. All these buccal mucoadhesion gels were subjected for the further evaluation. The mucoadhesion study results showed the detachment stress 0.5851±0.016, 0.6068±0.0134 and 0.6285±0.0128 dyne/cm^2 for GF N, GF 1 and GF 3 respectively. Better muchoadhesion was achieved in the nanosized curcumin buccal gel. Both the diffusion study, dissolution study and drug release kinetics showed that the better release rate was achieved in nanosized curcumin buccal gels compared to the native curcumin buccal gel and thus it can be concluded that by decreasing the curcumin size to nano range it has resulted in better drug release and effectiveness was also increased.

Keywords: Curcumin; Media Milling; Nanosuspension; Buccal Gel; Spresdiability; Mucoadhesive Gel

Introduction

Oral mucositis (oral inflammation) is a common toxicity of the gastrointestinal tract associated with anti-neoplastic therapies. In head and neck cancer patients, mucositis of the oral cavity and oropharynx is often severe and can be dose limiting and negatively impact quality of life and nutritional status [1]. Oral mucositis can affect patient's ability to maintain oral care, and the oral mucosa can have increased susceptibility to injury and local infection, increasing the risk for systemic infection [2]. The frequency and severity of mucositis varies with tumor type, radiation field and type, and dose and type of chemotherapy. Patients receiving radiotherapy with or without concomitant chemotherapy are at high risk of developing mucositis with a reported prevalence of nearly 100% [3]. This can be treated by local application of anti-inflammatory drugs, if nanoparticles are applied directly to the buccal mucosa, they are drained rapidly through the salivary actions, which leads to their rapid elimination through involuntary swallowing. Therefore, the development of mucoadhesive preparations for buccal administration of nanoparticles is desired [4]. Curcumin: Turmeric consists of dried and fresh rhizomes of the plant known as *Curcuma Longa linn.* belongs to the family *Zingiberaceae*. Curcumin is an active ingredient of turmeric which contain 2.85 to 6.14% w/w curcumin [5]. Chemically it is also known as diferuloylmethane. Curcumin shows anti-inflammatory, anti-oxidant, anti-carcinogenic property. It has the ability to suppress acute and chronic inflammation. Curcumin is freely soluble in organic solvents but practically insoluble in water [6]. It reduces the inflammation and activity of free radicals by inhibiting the action of pro-inflammatory cytokines. And it shows vulnerability to ultraviolet effect. Curcumin shows poor absorption, rapid metabolism and elimination. Oral absorption rate of curcumin is very less, only little amount of drug is absorbed into blood. biotransformation of drug takes place in the intestine. Curcumin shows good skin compatibility [7].

Nanosuspension

A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. Nanosuspension is a sub-micron colloidal dispersion of drug particles which are stabilized by surfactants, polymers or a mixture of both. They can also be defined as the biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. The nanosuspensions can also be lyophilized or spray dried and the nanoparticles can also be incorporated in a solid matrix. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose [8].

Potential benefits of nanosuspension technology for poorly soluble drugs

- Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, reduced variability, reduced fed/fast effects.
- Nanoparticles can adhere to the gastrointestinal/buccal mucosa prolonging the contact time of the drug and thereby enhance its absorption.
- A pronounced advantage of nanosuspension is that there are many administration routes for nanosuspensions such as oral, parenteral, pulmonary, dermal and ocular [9].

Nanosuspensions offers various advantages over conventional ocular dosage forms:

- Nanosuspensions have low incidence of side-effects by the excipients.
- Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.
- Increased resistance to hydrolysis and oxidation and physical stability..
- Reduced admn volumes; essential for intramuscular, subcutaneous, ophthalmic use.
- Finally, nanosuspensions can provide the passive targeting.

The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. Planetary ball Mills is one example of an equipment that can be used to achieve a grain size below 0.1 µm. A nanosuspension of Zn-insulin with the mean particle size of 150 nm was prepared using the wet milling technique. The major drawbacks of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product, degradation of thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥ 5 µm. In this work the bead milling is done using zirconium oxide beads in glass vial.

Advantages

- Simple technology.
- Low-cost process regarding the milling itself.
- Some extent it is a batch process.

Need for the study

Components of turmeric are named curcuminoids, which include mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin. All of these compounds are poorly soluble in water. It is well established in the literature that poor bioavailability is one of the leading causes of compound failure in preclinical and clinical development. Bioavailability of a compound depends on its solubility or dissolution rate. Dissolution may be the rate determining step for bioavailability and medicinal value therefore, efforts to increase dissolution rate for water insoluble drug is often needed. Nanosuspensions found to be promising methodology that can be used for enhancing the dissolution of poorly water soluble compounds with water insoluble and both water and lipid-insoluble drugs. These suspensions keep pharmaceutical active ingredient at the submicron levels in a liquid phase stabilized by added stabilizers. Preparation of nanosuspensions was reported to be a more cost effective and technically simple alternative and yield physically more stable product than liposomes. An alternative and most promising strategy to exploit science and technology at the nanometer scale is offered by the bottom-up approach, which starts from nano to subnano structures. The bottom-up approach is widely accepted in the area of nanoscience. Nano-suspensions play an important role in drug delivery system associated and nanotechnology. The basic challenge of this technique is that during the precipitation procedure the growth of the crystals needs to be

controlled by the addition of stabilizers to avoid agglomeration or aggregation that leads to the formation of microcrystals [10]. One of the delivery routes for which nanosuspensions can be applied is buccal route. Oral mucosa offers several advantages for drug delivery, such as high vascularization, promoting a systemic effect; the avoidance of first-pass metabolism; relatively low enzymatic activity, which could improve drug stability, drug release, skin permeation and bioavailability; and, therefore, patient compliance. Furthermore, drug administration to specific sites in the oral cavity constitute the common treatment of bacterial and fungal infections, toothaches, periodontal disease and others [11].

Hence, in this work, we propose to prepare and evaluate mucoadhesive buccal gel of native and nanosized curcumin.

Objectives

The objectives of the proposed study are:

- Selection of ideal experimental conditions for preparation of curcumin nanosuspension.
- Characterization of nanosuspension by particle size, zeta potential, PDI.
- Formulation of Buccal gels using suitable mucoadhesive polymers.
- Formulation of the curcumin nanosuspension loaded-gel (nanogel).
- Formulation of Buccal gels using native curcumin.
- Evaluation of prepared nanosuspension loaded buccal gel and native curcumin loaded gel for physical appearance, pH, spreadibility, drug content, *in vitro* drug release study, *in vitro* drug release kinetics and mucoadhesion, etc.

Materials and Methods

List of materials used

In the present study following materials were used from different sources Curcumin from Himalaya pvt ltd, HPMC E-15 from Lobachemie pvt ltd ,Mumbai, TWEEN 89,Sodium CMC,Carbopol934 were from sd fine chemicals, Mumbai and Yettria coated Zirconium beads of 0.4-0.6 mm from Synco Indusries Ltd, Jodhpur.

List of equipments used

Various Equipments were utilised to perform the entire experiments i.e. Digital balance, Rotary shaker, UV Visible Spectrophotometer, Diffusion cell, Magnetic stirrer, Hot Air Oven, pH meter, Dissolution test apparatus all are from college lab itself and Malvern Zeta sizer Nano ZS from Orchid Scientifics. Nasik

Methods

Determination of λmax of drug

A diluted solution of curcumin in phosphate buffer pH 6.2 was scanned for absorption maxima against blank between 200-800 nm using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The maximum absorbance was found to be 428 nm.

Calibration curve of curcumin

Accurately weighed curcumin (100 mg) was transferred into a 100 ml volumetric flask, dissolved and adjusted the volume up to 100 ml with methanol to get stock solution A. From the stock solution A, 10 ml was pipetted out into a 100 ml volumetric flask and volume was made up to mark with methanol to get stock solution B. From the stock solution B, known volume were pipetted out and made up to 10 ml with phosphate buffer (pH 6.2) in 10 ml volumetric flask to get 10- 100 µg/ml concentration solutions and absorbance was recorded at 428 nm by UV- visible spectrophotometer (UV-1601, Shimadzu, Japan). The study was performed in triplicate and results are reported as Mean ± sd (n = 3).

Preparation of curcumin nanosuspension

Media milling technique was adopted for formulation of Curcumin loaded nanosuspension by means of yettria-coated zirconium beads 0.4-0.6 mm (Synco Industries Ltd, Jodhpur, India) as milling agent. A wide mouth glass vial with outside diameter of 2.5 cm and inside diameter of 2.0 cm, and inside depth of 5.5 cm with total volume 5 mL was used in the milling process. Curcumin was evenly dispersed in an aqueous solution of stabilizer (HPMC E15) and surfactant (tween 80) followed by consequent addition of milling agent (zirconium oxide beads). This system was subjected to stirring on magnetic stirrer (Remi Labs, Mumbai, India) for specific period of time at the room temperature. The beads were filtered subsequently and Curcumin nanosuspension was used for further studies. The effect of stabilizer concentration and speed of rotation on formulation of nanosuspension was evaluated [16].

Particle size analysis

The particle size of prepared nanosuspensions was evaluated by using Malvern particle size analyzer [zeta sizer (nano-zs90)] nanosuspensions particles are suspended in the distilled water and one drop was placed on the slide and particle size was observed [12].

Zeta potential

Zeta potential was measured by determining the particle electrophoretic mobility using the Malvern particle size analyzer. These

measurements were performed at 25 °C using water as a dispersing medium and the nanosuspension was diluted in the ratio of 1:100 in distilled water [13].

Polydispersity index

Polydispersity index value was used to characterize the monodispersed and polydispersed nature of nanosuspension. Higher the value of Polydispersity index indicates the high value of non-uniformity [12].

Solubility of nanosuspension

Solubility of nanosuspensions were analysed in different solvents such as water, methanol and acetone respectively. Nanosuspension was dried in hot air oven (Consolidated Electrical Industries). Dried nanosuspension powder (equivalent 100 mg drug) was dissolved in 50 mL of these solvents respectively and kept in a rotary shaker for 48hrs, then filtered and absorbance was noted at 428nm in UV spectrophotometer (UV-1601, Shimadzu, Japan). The study was performed in triplicate and results are reported as Mean ± sd (n = 3) [13].

Mucoadhesion study

The mucoadhesive strength of prepared buccal gel formulations was determined using modified balance method. This equipment comprised a two-arm balance, one side of which contained two glass plates and other side contained a beaker.

The membrane used for mucoadhesive testing was fresh sheep buccal mucosa. Fresh sheep buccal mucosa was sprinkled by phosphate buffer (pH 6.8), then fixed using rubber band. The buccal gel was placed on the mucosal membrane fixed to the upper side of the lower plate and another was glued to the lower side of the upper plate using rubber band. The buccal gel was placed on the mucosal membrane fixed to the upper side of the lower plate. Then, the upper plate was placed over the lower plate and 5 g preload force (or contact pressure) was applied for 2 min (preload time). After removal of the preload force, the water was added slowly to the previously weighed beaker placed on the right hand pan until vial gets detachment stress in dyne/cm^2 was determined from the minimal weight that detaches the tissue from the surface of each formula using the following equation.

Detachment stress dyne/cm^2 = m.g/A Where,

m: The weight added to the balance in g,

g: The acceleration gravity 980 (cm/s^2) and A : Area of tissue exposed

The study was performed in triplicate and results are reported as Mean ± sd (n = 3) [14].

Drug content evaluation of nanosuspension:

Drug content of nanosuspensions were analysed in methanol. Nanosuspension was dried in hot air oven (Consolidated Electrical Industries). Dried nanosuspension powder (equivalent 100 mg drug) was dissolved in 50 mL of methanol and kept in a rotary shaker for 24hrs, then volume was made upto 100mL, filtered and absorbance was noted at 428nm in UV spectrophotometer (UV-1601, Shimadzu, Japan). The study was performed in triplicate and results are reported as Mean ± sd (n = 3) (15).

% Entrapment efficiency

This method is suitable for determining entrapment efficiency of nanosuspension when fairly high concentration of free drug is present in the supernatant after centrifugation. 10mL portion of the freshly prepared and cooled nanosuspension was centrifuged at 1000 rpm for ten minute using a Remi centrifuge. The supernatant was removed and the amount of unincorporated drug was measured by taking the absorbance of the supernatant solution at 428 nm by using UV spectrophotometer (UV-1601, Shimadzu). The study was performed in triplicate and results are reported as Mean ± sd (n = 3) (43).

EE % = [(Winitial drug – Wfree drug)/ Winitial drug] *100

Preparation of blank gel

Suitable polymers were tested for the preparation of buccal gel. Blank gels were prepared using the selected polymers i.e., carbopol 934 and sodium CMC in different concentration.

Selection of basic consistency of gel

The blank gels were prepared by varying the concentrations of the selected polymers, and basic consistency of the buccal gel was obtained by doing different trials. The formulation of buccal gel with good consistency were used for drug loading.

Drug loading of gel with native and nanocurcumin

- **Preparation of buccal gels containing native curcumin: R**equired quantity of curcumin was weighed and dispersered uniformly in prepared blank buccal gel by stirring on magnetic stirrrer to make 1% w/w curcumin gel. Curcumin loaded buccal gel formulation was prepared in triplicate.

- **Preparation of buccal gels loaded with curcumin nanosuspension:** The required quantity of nanosuspension of curcumin was dispersed uniformly in buccal gel to get 1% w/w gel. Curcumin loaded buccal gel formulation was prepared in triplicate.

Evaluation of buccal gel

Physical appearance

Gel formulations were visually inspected for clarity, color, homogeneity, consistency, and presence of particles [14].

Spreadability

A sample of 0.1g of each gel was pressed between two slides with 500g weights for about 5 min where no more spreading was expected. Diameters of spread circles were measured in cm and were taken as comparative values for spreadability (diameter of the spread circle initial diameter). The study was performed in triplicate and results are reported as Mean ± sd (n = 3) [14].

In vitro drug release study

The drug release studies of prepared formulations were carried out using USP paddle dissolution test apparatus at 50 rpm and 37 ± 1°C using 900 ml using phosphate buffer solution (pH 6.2). Drug release was determined collecting samples at different time intervals (0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h and 6h). An aliquote of 5 ml was collected from receptor compartment and replaced with fresh medium each time. The obtained sample was filtered in membrane filter (0.22µm) and analyzed by using UV spectrometer at 428 nm. The amount of drug released was obtained from the standard plot. The study was performed in triplicate and results are reported as Mean ± sd (n = 3).

In vitro drug release kinetics

The data obtained from *in vitro* release study was fitted to various kinetic equations to find out the mechanism of drug release from buccal gel. In order to analyse the drug release mechanism the data was fitted to zero order, first order, higuchi and korsmeyer-peppas model. The study was performed in triplicate and results are reported as Mean ± sd (n = 3).

Discussion

In the present work buccal mucoadhesive gels of curcumin nanosuspension were prepared by using a different ratio of sodium CMC and carbopol 934 as gelling agents.

Determination of λmax of drug

A diluted solution of curcumin in phosphate buffer solution (pH 6.2) was scanned for absorption maxima against blank between 200-800nm using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The maximum absorbance was found at 428nm. The absorbance values were shown in Table 1.

Sl. No.	Concentration (µg/ml)	Absorbance (at 428 nm)
0	0	0
1	2	0.023 ± 0.031
2	4	0.045 ± 0.1
3	6	0.079 ± 0.12
4	8	0.1 ± 0.012
5	10	0.13 ± 0.26
6	12	0.15 ± 0.63
7	14	0.18 ± 0.54
8	16	0.23 ± 0.32
9	18	0.26 ± 0.12

Table 1: Calibration curve of Curcumin in phosphate buffer solution (pH 6.2).
Values are mean ± SD, n = 3.

Calibration curve of curcumin

The calibration curve of curcumin was developed in the concentration range of 2-18µg/ml at wavelength 428 nm. Good linearity with regression coefficient of 0.9911 (R2 value) was observed in the tested concn range, it obeyed Beer-Lambert's law (Figure 1).

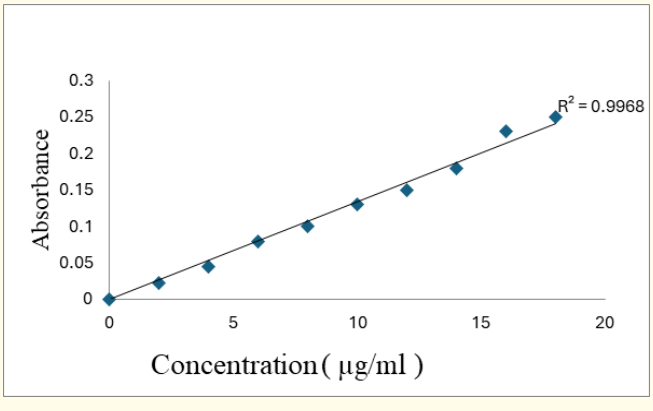

Figure 1: Calibration curve of Curcumin in phosphate buffer solution (pH 6.2).

Preparation of curcumin nanosuspension

Curcumin nanosuspension was prepared by media milling technique as reported previously . HPMC E15 and tween 80 were selected as stabiliser and surfactant respectively. Drug to stabiliser ratio was selected for the preparation of nanosuspension by using different concentration of stabiliser, bead volume and rpm. All the formulations are tabulated.

Native Curcumin dispersed in water vs Curcumin nanosuspension

The difference between native curcumin dispersed in water and the nanosupension were analysed visually and it was evident that native curcumin had least solubility (negligible) in water, while the nanosuspension was a well dispersed.

Evaluation of nanosuspensions

Characterisation of nanosuspensions.

Particle size analysis

Particle size is the fundamental property of the sedimentary materials. Measurement of the particle size was required to confirm the formation of particles in the nano range. Particle size of the nanosuspensions was measured by dynamic light scattering technique using Malvern zeta sizer nano ZS (Malvern Instruments, UK) at 25 °C. The particle size of the curcumin nanosuspn formulations were in the range of 148-334 nm as shown in (table 3).

Zeta potential

Zeta potential ZP (±) is an electro kinetic potential in colloidal dispersions. Zeta potential is key indicator in the stability of the nanosuspension. It refers to the surface charges of the particles; magnitude of the zeta potential indicates degree of electrostatic repulsion between adjacent and similarly charged particles in dispersion. High zeta potential refers to the high stability of nanosuspensions. The zeta potential is small the attractive forces may exceeds this repulsion and the dispersion may break and flocculate. Therefore the zeta potential is a useful parameter to predict the physical stability of the nanosuspension. The result showed that the nanosuspensions were negatively charged and ZP was in the range of -11.07 to -18.3 mV shown in (table 3).

Poly dispersability index (PDI)

Polydispersity index was measured by using Malvern zetasizer-nano ZS. PDI was used to estimate the average uniformity of the nanosuspension. PDI measurement was essential to confirm the narrow size distribution of the particles. And larger PDI value corresponds to a larger size distribution in the particle sample. PDI also indicate the nanoparticle aggregation along with the consistency and efficiency of particle surface modifications throughout the particle samples. PDI indicate the monodispersed and polydispersed nature of the samples. The PDI of nanosuspensions loaded with curcumin were in the range of 0.20 to 0.31 shown in (table 2). The average particle size was found to be less than 0.5 and PDI was less than 0.350, hence it indicates that all the formulations were in narrow size distribution.

Formulation	PS (nm)	ZP (mV)	PDI
F1	193.4	-15.1	0.214
F2	191.3	-13.7	0.208
F3	154.9	-18.3	0.229
F4	148.5	-13.0	0.220
F5	334.9	-11.7	0.310
F6	196.4	-13.5	0.200
F7	287.2	-13.4	0.21
F8	174.3	-13.7	0.225

Table 2: Characterization of Nanosuspension.

*PS- Particle size, PDI- Polydispersity index, ZP- Zeta Potential.

Formulation F1 and F3 were selected for the further study due to their lower particle size distribution, better zeta potential and PDI value. Tabulated in table 3.

Table 3: Drug Content, Spreadability, pH mucoadhesion analysis of the native and optimized formulations.

Formulation	Mean ± SD			
	Drug content (mg)	Spreadability (cm)	pH	Mucoadhesion Dyne/cm^2
GF N	43 ± 0.20	2.76 ± **0.057**	6 ± **0.1**	0.5851 ± **0.016**
GF 1	46 ± 0.11	2 ± **0.1**	6.16 ± **0.057**	0.6068 ± **0.0134**
GF3	47.5 ± 0.2	2.26 ± **0.057**	6.1 ± **0.173**	0.6285 ± **0.0128**

Solubility of nanosuspension

Solubility of nanosuspension formulations ranged from 0.64 ± 0.13 mg to 0.85 ± 0.18 mg in water, 1.73 ± 0.03 mg to 1.87 ± 0.22 mg in acetone and 1.17 ± 0.83 mg to 1.48 ± 0.26 mg in methanol. The formulation F3 showed highest solubility.

Mucoadhesion study

The mucoadhesion strength is one of the most important physicochemical parameters for prolonging mucoadhesive retention time and thereby better therapeutic effects of the mucoadhesive polymer. The degree of mucoadhesion depends on concentration of polymer, degree of hydration, polymer chain length, and molecular weight of the polymer.

There was directly proportional effect of polymer concentration on mucoadhesive strength, so mucoadhesive strength of the formulation was taken as one of the dependent parameter for optimization of formulation The results were shown in Table 3.

The *in vitro* drug release by diffusion

The *in vitro* drug release study was done using franz diffuision cell apparatus. Dialysis membrane was soaked in phosphate buffer solution (pH 6.2) before its utilization for diffusion study. 1 gm of prepared buccal gel formulations GF N, GF 1 and GF 3 were placed in donor compartment and phosphate buffer solution (pH 6.2) was filled in receptor compartment. Dialysis membrane was kept between donor and receptor compartment as a diffusion membrane and tightened using clamp. The temperature of receptor compartment media was maintained at 37 ± 10C at 300 rpm. 3 mL aliquots of sample was collected at regular time intervals (0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h) and sink condition was maintained by replacing receptor compartment with fresh media. The collected samples were observed using UV visible spectrophotometer and cumulative drug release from the formulations were evaluated. The buccal gel loaded with native curcumin GF N showed the drug release of 18.701 ± 0.02 by the end of 6 hrs. The optimized buccal gels GF 1 and GF 3 showed the cumulative drug release of 54.814 ± 0.14and 57.81 ± 0.065 respectively The absorbance values were shown in Table 4. By this we can say that GF 1and GF 3 had greater drug release when compared with GF N (Figure 2).

The in vitro drug release by dissolution

In the dissolution study, the drug release from the formulation GF N, GF1 and GF3showed 20.30 ± 0.021, 69.49 ± 0.001 and 77.24 ± 0.022% of drug release at the end of 6 h respectively showed in (Figure 2). Formulation GF 1 and GF 2 showed the highest drug release compare to GF N because of smaller particle size of the nanosuspensions showed in the (Table 5). Drug release is directly depend on the particle size. Formulation GF N showed the less drug release compare to GF 1 and GF 2 formulations because it was not subjected to media milling. Media milling reduces the particle size and this confirms that particle size will affect the drug release from the buccal gel loaded with nanosuspensions.

Table 4: The *in vitro* drug release by Diffusion.

Time (h)	% Cumulative drug release		
	GF N	GF 1	GF3
0	0	0	0
1	1.892 ± 0.12	4.532 ± 0.021	4.745 ± 0.04
1.5	3.910 ± 0.01	6.857 ± 0.022	7.55 ± 0.82
2	3.945 ± 0.002	9.546 ± 0.1	14.32 ± 0.13
2.5	6.449 ± 0.21	17.57 ± 0.034	20.56 ± 0.42
3	9.113 ± 0.03	22.57 ± 0.065	26.61 ± 0.032
4	12.136 ± 0.13	33.64 ± 0.14	38.54 ± 0.12
5	15.302 ± 0.08	45.21 ± 0.031	45.96 ± 0.17
6	18.701 ± 0.02	54.814 ± 0.14	57.81 ± 0.065

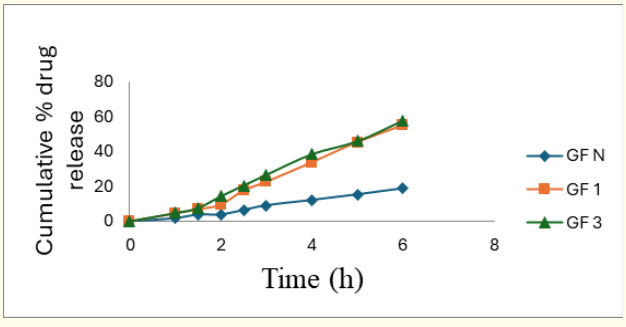

Figure 2: The *in vitro* drug release study by diffusion.

The in vitro drug release kinetics

The data obtained from *in vitro* drug release study was fitted to various kinetic equations to find out drug release mechanism from the buccal gels. A correlation co-efficient (R2) was choosed to define the approximation accuracy of an individual model. From the release kinetic (Table 6) the GF N and GF 3 has shown Zero order drug release and GF 1 has shown 1st order drug release and

Table 5: Results of *in vitro* drug release from the formulations GF N, GF 1 and GF3.

Time (h)	% Cumulative drug release		
	GF N	GF 1	GF 3
0	0	0	0
1	9.109 ± 0.009	13.28 ± 0.0008	19.8 ± 0.006
1.5	10.69 ± 0.018	24.22 ± 0.006	25.4 ± 0.005
2	11.08 ± 0.020	31.15 ± 0.0065	32.6 ± 0.011
2.5	12.24 ± 0.020	37.03 ± 0.006	40.24 ± 0.014
3	13.95 ± 0.023	42.80 ± 0.003	49.52 ± 0.017
4	15.78 ± 0.022	52.18 ± 0.003	57.2 ± 0.021
5	17.41 ± 0.023	61.47 ± 0.002	65.24 ± 0.024
6	20.30 ± 0.021	69.49 ± 0.001	77.24 ± 0.022

Table 6: Mechanism of kinetics of *in vitro* drug release study.

Mechanisms and kinetics of *in vitro* drug release study				
Formulation	Regression co-efficient (R^2)			Koresmeyer - peppas equation (n)
	Zero order	First order	Higuchi	
GF N	0.9922	0.9214	0.95096	0.9361
GF 1	0.9772	0.9880	0.98838	1.387
GF 3	0.9159	0.9086	0.99397	1.3339

it is observed that Korsemeyers Peppas values of GF N was 0.9361 which is less than 1 and thus it follows non-fickian transport (anamalous diffusion). And gel formulations GF 1 and GF 3 has n value greater than 1.0 (Super Case II transport) suggest a drug release process dependent on the relaxation of the polymer chains in the matrix, passing from a vitreous state (lower kinetic movement and increased potential energy) to a relaxed state rubber type (high kinetic movement and lower potential energy).

Summary

The present study was aimed at the comparision of the buccal gels prepared from native and nanosized curcumin. This formulation is used in the treatment of oral mucositis (oral inflammation). The main objective of the present work was to prepare curcumin nanosuspension in order to improve its solubility and bioavalability by using media milling technique to improve the patient compliance. The prepared nanosuspensions were characterized for various parameters like particle size, polydispersity index and zeta potential. The particle size of the native curcumin, optimized formulation F1 and F3 were 4406 nm, 193.4 nm and 154.9 nm respectively. The PDI of native curcumin, optimized formulation F1 and F3 were 0.480, 0.214 and 0.229 respectively. And the zeta potential value of native curcumin and selected formulation F1 and F3 were -42.3 mV, -15.1 mV and -18.3mV respectively. The native curcumin and nanosuspensions were also evaluated for solubility studies, drug content, % entrapment efficiency. The formulations F1 to F8 showed greater solubility in acetone followed by methanol followed by water. The drug content of F1 to F8 were in the range 42.93 ± 0.024 to 48.24 ± 0.023, and the formulation F1 had shown higher drug content. The % EE of formulations F1 to F8 ranged between 65 ± 0.216 to 72.3 ± 0.224, and the formulation F1 has shown higher % EE. Buccal mucoadhesive gels were prepared by incorporation native curcumin and selected nanosuspension of curcumin. The prepared buccal mucoadhesive gels of curcumin were evaluated for their physical appearance, spreadability, drug content, pH, Mucoadhesion, *in vitro* drug release, *in vitro* drug release kinetics and invitro permeation study. The drug content of the buccal gel formulations ranged between 43 ± 0.20mg to 47.5 ± 0.2mg. The

spreadability analysis says that all three gel formulations ranges between 2 ± 0.1 cm to 2.76 ± 0.057 cm, where formulation GF N .had shown higher spreadability. The pH values of the formulations GF N, GF 1 and GF 3 were ranged between 6 ± 0.1 to 6.16 ± 0.057, the pH of all formulations were within the acceptable range. The mucoadhesion values of all the buccal formulations GF N, GF 1 and GF 3 showed the detachment stress ranged between 0.5851 ± 0.016 dyne/cm^2 to 0.6285 ± 0.0128 dyne/cm^2, which shows that the mucoadhesion was good in all three formulations. The % cumulative drug diffusion obtained of formulations GF N, GF 1 and GF 3 was 18.701 ± 0.02, 54.814 ± 0.14 and 57.81 ± 0.065 % respectively, and the drug release from GF N had shown less drug release compared to that of the optimized formulations. The % cumulative drug release obtained by vitro dissolution studies of formulations GF N, GF 1 and GF 3 had shown the drug release of 20.30 ± 0.021, 69.49 ± 0.001 and 77.24 ± 0.022 respectively, and the drug release from GF N had shown less drug release compared to that of the optimized formulations. The formulations GF N and GF 3 had shown Zero order drug release and GF 1 has shown 1st order drug release and it is observed that Korsemeyers Peppas values of GF N was 0.9361 which is less than 1 and thus it follows non-fickian transport (anamalous diffusion). And gel formulations GF 1 and GF 3 has n value greater than 1.0 (Super Case II transport) suggest a drug release process dependent on the relaxation of the polymer chains in the matrix, passing from a vitreous state (lower kinetic movement and increased potential energy) to a relaxed state rubber type (high kinetic movement and lower potential energy). was filled in receptor compartment. Dialysis membrane was kept between donor and receptor compartment as a diffusion membrane and tightened using clamp. The temperature of receptor compartment media was maintained at 37 ± 10C at 300 rpm. 3 mL aliquots of sample was collected at regular time intervals (0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h) and sink condition was maintained by replacing receptor compartment with fresh media. The collected samples were observed using UV visible spectrophotometer and cumulative drug release from the formulations were evaluated. The buccal gel loaded with native curcumin GF N showed the drug release of 18.701 ± 0.02 by the end of 6 hrs. The optimized buccal gels GF 1 and GF 3 showed the cumulative drug release of 54.814 ± 0.14and 57.81 ± 0.065 respectively. By this we can say that GF 1and GF 2 had greater drug release when compared with GF N (Figure 3).

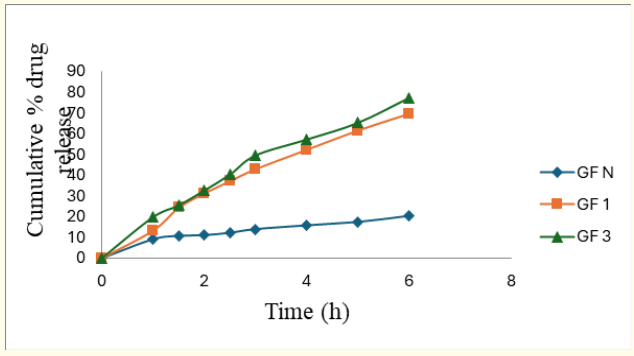

Figure 3: The *in vitro* drug release from the formulations GF N, GF 1 and GF3.

The *in vitro* drug release by dissolution:

In the dissolution study, the drug release from the formulation GF N, GF1 and GF3showed 20.30 ± 0.021, 69.49 ± 0.001 and 77.24 ± 0.022% of drug release at the end of 6 h respectively showed in (Figure 3). Formulation GF 1 and GF 3 showed the highest drug release compare to GF N because of smaller particle size of the nanosuspensions showed in the (Table 5). Drug release is directly depend on the particle size. Formulation GF N showed the less drug release compare to GF 1 and GF 3 formulations because it was not subjected to media milling. Media milling reduces the particle size and this confirms that particle size will affect the drug release from the Buccal gel loaded with nanosuspensions.

The *in vitro* drug release kinetics

The data obtained from *in vitro* drug release study was fitted to various kinetic equations to find out drug release mechanism from the buccal gels. A correlation co-efficient (R2) was choosed to define the approximation accuracy of an individual model. From the release kinetic (Table 6) the GF N and GF 3 has shown Zero order drug release and GF 1 has shown 1st order drug release and it is observed that Korsemeyers Peppas values of GF N was 0.9361 which is less than 1 and thus it follows non-fickian transport (anamalous diffusion). And gel formulations GF 1 and GF 3 has n value greater than 1.0 (Super Case II transport) suggest a drug release process dependent on the relaxation of the polymer chains in the matrix (Table 6), passing from a vitreous state (lower kinetic movement and increased potential energy) to a relaxed state rubber type (high kinetic movement and lower potential energy).

Conclusion

In this study, Curcumin nanosuspensions were prepared using media milling technique. HPMC E15 and tween 80 were used as stabilizer and surfactant respectively. By varying the stabilizer ratio, bead volume and RPM eight different nanosuspension formulations were formulated . F1 and F3 were selected for the further studies due to their higher stability rate among prepared formulations. Buccal gels with 1:1 ratio of Sodium CMC and Carbopol 934 was selected for the further drug loading. Buccal gels were then loaded with native and nanosized curcumin and were named as GF N, GF 1 and GF 2, respectively. All these buccal mucoadhesion gels were subjected for the further evaluation. Better muchoadhesion was achieved in the nanosized curcumin buccal gel. The *in vitro* drug release studies showed that the better release rate was achieved in nanosized curcumin loaded buccal gels compared to the native curcumin loaded buccal gel and thus it can be concluded that by decreasing the curcumin size to nano range it has resulted in better drug release and effectiveness was also increased.

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