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RESEARCH ARTICLE

# The Electro-Spun Sublingual Film Containing Curcumin Micelles

**Chelsi Patel, Rahul Pujari, Pankita Rede, Bijal Prajapati and Abhay Dharamsi**

Department of Pharmaceutics and Pharmaceutical Technology, Parul Institute of Pharmacy, Parul University, Vadodara - 391760, Gujarat, India; chelsip2003@gmail.com

## Abstract

Hydrophilic polymers D-tocopheryl polyethylene glycol succinate (TPGS-1000) and Poloxamer-188 were combined for the formulation of a sublingual film that aids in improving the oral bioavailability of the drug curcumin, which is not very soluble. For the formulation of micelles, the thin-film hydration technique was used and then electro-spun into a sublingual film that contained 13 % w/v PVP. Following that, prepared micelles and films were assessed and evaluated (particle size, PDI, zeta potential, %EE, pH studies, disintegration time, and *in vitro* drug release). According to the findings, the average particle size of the blended micelles was 230.2 nm. The ideal formulation of mixed micelles had a mean zeta potential and PDI of 20.73 mV and 0.258±0.038, respectively. Additionally, an entrapment efficiency of 82% was reached. In an aqueous medium, the film disintegrated in 40±10 seconds. Micelles were incorporated into the film without losing their integrity. Importantly, as compared to a pure drug, the films with micelles put on them showed improved bioavailability, high permeability and rapid absorption of the curcumin. Compared to the pure drug, the bioavailability of the films was increased by around 2.18 times due to the presence of mixed micelles loaded with curcumin. The results also showed that micelles-loaded sublingual films performed well *in vitro* for bioavailability improvement. In the end, it was found that films containing a mixture of poloxamer-188 and TPGS-1000 micelles would function effectively as carriers to boost curcumin's bioavailability.

**Keywords:** Electro Spinning, Micelles, Poloxamer-188, Sublingual Film, TPGS

## 1. Introduction

The most utilised phytonutrient in the food business is curcumin (Cur). It is made from the rhizomes of the turmeric plant, *Curcuma longa* L. *Curcuma longa* L. belongs to the family Zingiberaceae. It has a wide range of medicinal characteristics, including anti-inflammatory effects, anticancer, and other properties[1]. Numerous experimental findings have conclusively demonstrated that curcumin can cause the destruction and/or apoptosis of human cancer cells derived from a variety of solid malignancies, including colorectal, lung, breast, pancreatic, and prostatic carcinomas[2-6].

Curcumin's ability to slow the spread of cancer at several organ sites was recently proven by a clinical experiment conducted on people with familial adenomatous polyposis, demonstrating the possibility of chemoprevention[7]. Numerous studies also revealed that curcumin was a safe and effective substance for chemotherapy and cancer treatment. Its low water solubility and alkaline pH-induced breakdown, however, reduce its bioavailability[8,9]. Only a trace of the substance is detected in the blood after oral ingestion (up to 8 g per day)[10].

Utilizing the right administration methods to promote the rate at which curcumin is absorbed in the upper GI tract is one effort to increase its bioavailability. Especially

*Author for correspondence

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polymeric micelles, a nano drug delivery method holds promise for oral administration. By encapsulating a hydrophobic medication in the cores of polymeric micelles, which have internal and external regions known as the "core" and "shell", respectively, significant benefits are provided for enhancing the oral absorption of the chemotherapeutic treatment[11,12]. It can shield the medicine from direct contact with the gastrointestinal (GI) contents, which would cause metabolic breakdown and chemical breakdown, and deliver the medicine at a concentration higher than its natural water solubility to the desired location. In the meantime, the medication was sustainedly delivered and directly absorbed by cells. In comparison to polymeric micelles for drug delivery, mixed micelles have increased physical stability, improved drug-loading capabilities, and improved antidilution ability, it should be noted[13].

Block copolymers with two or more comparable structural elements can self-assemble into mixed micelles. By using their constituent copolymers, mixed micelles can produce micelles with diverse functionalities. To administer curcumin, a mixed micelle was created using Poloxamer 188 and TPGS 1000. Additionally, the size, and structural characteristics of micelles aid in enhancing absorption through biological barriers[14]. By enhancing the physical stability of the micelles and enabling high drug loading, the various hydrophilic and lipophilic mixed micelle molecules offer considerable advantages in oral medication administration[15]. To produce stable formulations, micelles must solidify[16]. To avoid expensive lyophilizing or spray-drying procedures, mixed micelles are designed to be incorporated into oral films. Micelles incorporated sublingual films to offer a creative drug delivery method for the improvement of the bioavailability of medications that are not well-soluble in water[17].

Importantly, giving medication via the oral mucosal route can prevent drug breakdown in the gastrointestinal tract. For quick drug delivery, an alternative to the orally ingested is the sublingual method[18]. The sublingual route of medication delivery was deemed suitable since acute allergic responses require prompt treatment. Sublingual films would penetrate more deeply if micelles were present. Micelles may therefore be an effective and cost-effective strategy to get over the physiological barriers and obtain the necessary bioavailability of curcumin[19].

The formulation of the desired drug delivery system can benefit greatly from the thoughtful selection of amphiphilic compounds[20]. Poloxamer 188 was chosen over other High-Molecular-Polymers (HMPs) because it produces micelles of manageable size and has adequate stability[21,22]. Poloxamer-188 is additionally less mucoadhesive than HMPs. Poloxamer-188 has a lower molecular weight than HMPs, which promotes faster drug release[23]. The Critical Micelle Concentration (CMC), suggests that the concentration of poloxamer-188 for the creation of micellar systems ranges between 0.04 and 0.46 mM. The integrity of the cell can be preserved by using poloxamer-188 to reseal damaged cell membranes[24]. Poloxamer-188 also demonstrated reduced toxicity in earlier investigations when compared to other HMPs[25]. It is generally known that poloxamer-188 works to make medications that are not very soluble to more soluble[26]. Additionally, an FDA-approved biological modification called D-tocopheryl polyethylene glycol succinate 1000 (TPGS) is used in nano-carrier systems to deliver drugs that are not easily soluble[27]. While blocking efflux transporters, particularly p-glycoprotein, the TPGS-1000 enhances oral absorption and stabilises sublingual films[28]. Curcumin was successfully delivered to the brain using TPGS-1000 micelles[29,30]. In the past, the combined micelles of poloxamer-188 and TPGS-1000 have been employed to transport medications[31]. In this investigation, amphiphilic compounds are kept at a concentration considerably above their CMC TPGS-1000 has a CMC value of around 0.02 mM[32]. Because they have advantages in terms of biocompatibility, stability, high entrapment efficiency, and high-water solubility capability[33], poloxamer-188 and TPGS-1000 are suitable candidates to serve as boost the bioavailability of medicines with limited solubility.

For the enhancement of curcumin bioavailability, this work aimed to formulate novel sublingual films for mucosal delivery that contained TPGS-1000 and poloxamer-188 mixed micelles. This improves absorption and for stabilisation, encapsulated micelles can be incorporated into sublingual films. The purpose of the current formulations was carefully described in order to assess the degree of improvement in curcumin bioavailability[34].

## 2. Materials and Methods

### 2.1 Materials

Curcumin was gifted from Suncure, Vadodara for this research work. Simson Pharma Limited, Mumbai, Gifted Poloxamer-188. PVA was purchased from

Qualikems Fine Chem, Vadodara, while TPGS-1000 was provided by SD Fine Chem Ltd. in Mumbai. The supplier of potassium dihydrogen phosphate was Fischer Scientific in Mumbai. Other chemicals and reagents employed were of analytical grade.

## 2.2 Preparation of Micelles

Thin-film hydration was used to formulate curcumin micelles (Figure 1). Different ratios of curcumin, Poloxamer-188, and TPGS-1000 were dissolved in ethanol using a round-bottom flask (Table 1). This round-bottom flask was then attached to a rota evaporator (Rotavapor-R-300®, Buchi Labortechnik AG, Flawil, Switzerland) to produce a thin layer of polymers.

10 mL of distilled water was added to the mixture to hydrate the film after one hour of magnetic stirring at 200 rpm and 50°C temperature to form micelles. Each formulation of micelles included 10 milligrams of curcumin[34].

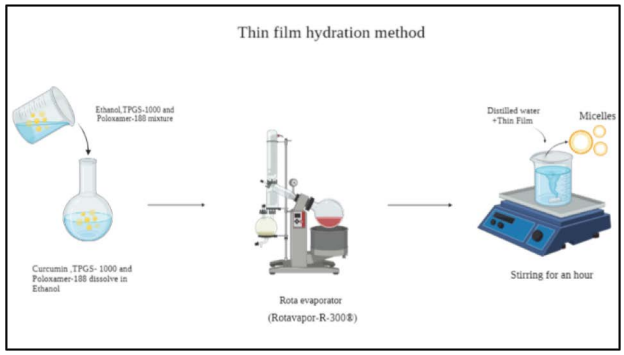


**Figure 1.** Method of preparation of Micelles.

**Table 1.** Composition of formulations for preparation of micelle

| Formulation | Curcumin (mg) | Poloxamer -188 (mg) | TPGS 1000 (mg) |
|---|---|---|---|
| F-1 | 10 | 100 | 50 |
| F-2 | 10 | 50 | 150 |
| F-3 | 10 | 150 | 50 |
| F-4 | 10 | 100 | 50 |
| F-5 | 10 | 50 | 100 |
| F-6 | 10 | 50 | 200 |
| F-7 | 10 | 100 | 50 |
| F-8 | 10 | 100 | 100 |
| F-9 | 10 | 150 | 150 |

## 2.3 Formulation of Sublingual Films Loaded With Curcumin Micelles

The above-prepared Micelles were added to the polymeric solution, which contains 13 % w/v PVA, to create polymeric micelles. The 5 ml syringe was then filled with the polymeric solution, the flow rate of the syringe pump was set to 10 mL/min and 18.5 KV voltages were applied to the needle. The drum speed was between 250 and 350 rpm, and the distance between the needle and collector was 15 cm. Curcumin micelles loaded nanofibers were created on the collecting drum. These nanofibers were collected, examined, and characterised further[35].

## 2.4 Characterization of Prepared Micelles

Characterization of the Micelles with UV Spectroscopy and Zeta Sizer can be their distinguishing features.

### *2.4.1 Particle Size Distribution Measurement*

To determine particle size distribution, a Zeta Sizer was utilised (Nano ZS 90, Malvern Instruments UK). The material was examined at a scattering angle of 90° at 25 °C[32].

### *2.4.2 Percentage Entrapment Efficiency (% EE)*

For the evaluation of the entrapment efficiency of prepared micelles, drug-loaded micelles were centrifuged at 15000 rpm for 30 minutes to separate the supernatant. A UV detector was used to evaluate the supernatant after it had been collected and dissolved in ethanol. Calculating the drug concentration at 424 nm to determine the total amount of drug contained within the micelles[15,18]. The given formula was used to determine the entrapment efficiency:

$$\%\mathbf{EE} = \frac{\textbf{Drug content in the product}}{\textbf{total amount of drug (mg)}} \times 100$$

## 2.5 Micelles-loaded Sublingual Film Characteristics

### *2.5.1 Surface pH*

Surface pH was determined using a digital pH meter (Equiptronics, EQ-611, Mumbai, India) to check whether the film causes irritation to the oral mucosa. Films were placed in closed Petri plate containing 5 ml distilled water. After moistening, pH probe was placed

in close contact with the wetted films, and the surface pH was identified in triplicate. It is necessary that films should have nearly uniform and neutral pH value[36].

#### 2.5.2 Thickness of the Sublingual Film

Costs and coating quality can be impacted by the thickness of the film. Coating thickness can be assessed with a variety of tools and is crucial for maintaining product quality, process control, and cost control[4]. A Vernier Caliper was used to measure the film thickness at three separate locations, and the average was calculated.

#### 2.5.3 Folding Endurance of Film

The number of folds was counted after folding the oral films repeatedly in the same direction. The endurance value of each film was determined by the number of folds without breaking.

#### 2.5.4 Disintegration Time

For disintegration, the required size of films was placed in the beaker containing 10 ml of pH 6.8 buffer to mimic saliva. The Disintegration time was noted for each film at which film started to break apart. All the studies were performed in triplicate for each batch[37].

#### 2.5.5 Surface Morphology by SEM

The Scanning Electron Microscope (SEM) is a common method for observing the morphology and microstructure of materials. An electron beam with low energy is sent to the material and used in SEM to scan the surface of the sample.

#### 2.5.6 In-vitro Drug Diffusion Study

Using a dialysis bag, the prepared batch of micelles was tested for in-vitro drug release. The release media (pH 7.4) employed was simulated saliva[35]. At 100 rpm and 37°C, micellar suspensions were re-dispersed in 1 mL of simulated saliva fluid and shaken using an orbital shaker. At set intervals, 2 mL of a sample was taken. An equivalent amount of newly generated simulated saliva fluid was used in place of the release medium. The concentration of curcumin in all samples was determined using a UV-Visible method method at a wavelength of 424 nm.

## 3. Results

### 3.1 Entrapment Efficiency, Zeta Potential, and Particle Size

Poloxamer-188 and TPGS-1000 mixed micelles that were loaded with curcumin had an average size of 230.2 nm and an average PDI value of 0.258 ± 0.038. With a PDI value of 0.262 ± 0.023, the particle size following sublingual film dispersion was 250.2 nm, indicating a narrow size distribution. After the film was re-dispersed, there was a slight increase in particle size. Micelles had an average surface charge of 20.73 mV. In the cases of the F-5, F-6, and F-7 micelle formulations, the entrapment efficiency was high. With an increase in the micelles-forming components (TPGS-1000/ poloxamer-188) above the CMC value, the % EE increased. The drug loading values ranged from 4.8 to 10.61 ± 2 %. The findings demonstrate that the size of the micelles did not considerably alter after being incorporated into the films.

### 3.2 Surface pH

The surface pH of the film was found to be in the range of 6.925 ± 0.045 pH, which is near neutral pH, and it shows that it is not producing any irritation on sublingual mucosa, which is why it is more acceptable and has better compliance with the patient.

### 3.3 Thickness

Vernier Calliper is used to measure the thickness of the film, which was found to be 0.002±0.04 – 0.010±0.01 mm.

### 3.4 Folding Endurance

The folding endurance of Curcumin micelles-loaded film was found to be 320 ± 10, which shows the good mechanical strength of the film.

### 3.5 *In Vitro* Disintegration Time

Disintegration time was within the range of 40 ± 10 seconds for curcumin film. All of the films had been dissolved within one minute.

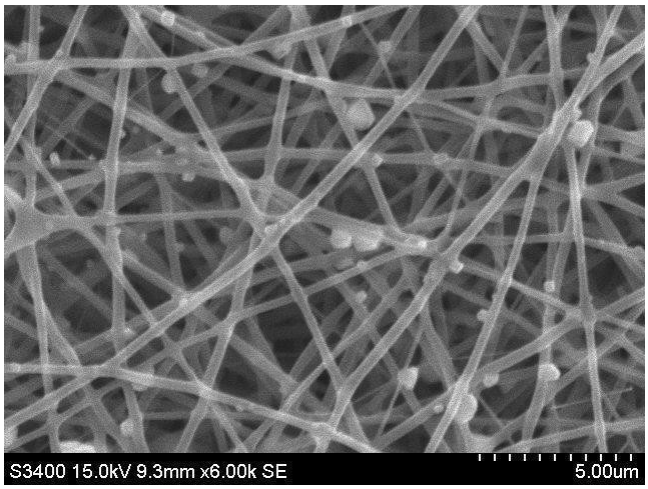


**Figure 2.** Surface morphology by SEM**.**

### 3.6 Surface Morphology by SEM

A scanning electron microscope was used to examine the surface morphology of curcumin micelles. Figures 2 and 3 shows the surface morphology by SEM and it was photographed at 5 µm.

### 3.7 *In Vitro* Dissolution Studies

Figure 3 depicts the in vitro release of curcumin, curcumin loaded film and curcumin micelles-loaded films (F1 to F9). The percentage of drugs released within the first 35 minutes from sublingual films (Cur. Loaded film, F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9) was 70 %, 75%, 88%, 99%, 81%, 100%, 92%, 55%, 62%, and 72%, respectively. As opposed to this, Curcumin released roughly 40 % of its whole amount within 30 minutes ($p < 0.05$). The drug from the micelles-loaded film (F-5) was released above 75% within 5 minutes, whereas just 29.5 % of the medication was dissolved in 5 minutes from the Curcumin loaded Film.

## 4. Discussion

The micelles components have an impact on the drug loading and entrapment effectiveness, which are accountable for the increased drug loading and entrapment effectiveness. The hydrophilic head group and lipophilic core of micelles held the medicine[35]. The proportion of TPGS-1000 to poloxamer-188 in their mass concentrations had a considerable impact on the effectiveness of micelle entrapment. By adjusting the

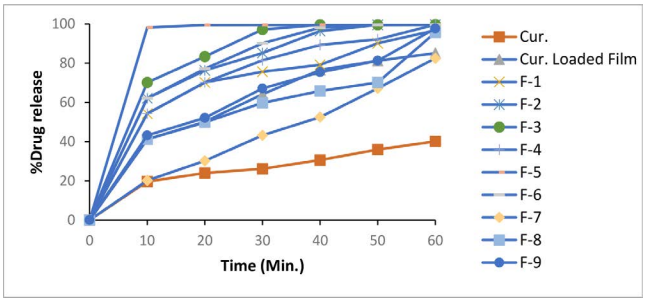


**Figure 3.** *In vitro* drug release profiles of Curcumin, Curcumin loaded film, and Curcumin micelles loaded Sublingual films.

concentrations of TPGS-1000 and poloxamer-188, the effects of the mass concentration ratio were assessed. Entrapment Efficiency (EE) of micelles was significantly enhanced when the concentration of TPGS-1000 was raised while maintaining the concentration of poloxamer188. On the other hand, by raising the concentration of poloxamer-188 while maintaining the same concentration of TPGS-1000, the percent EE was reduced to continue research, and TPGS-1000/ poloxamer-188 was diluted. Additionally, the total concentration of TPGS-1000 and poloxamer-188 influenced the efficiency of curcumin entrapment. By increasing the combined concentration of TPGS-1000 and poloxamer-188 from 50 mg to 150 mg, the entrapment efficiency was markedly improved. Curcumin at a dosage of 10 mg/mL produced small, stable micelles.

The incorporation of curcumin into the hydrophobic core of micelles enhanced the substance's solubility. In comparison to pure drug and curcumin-loaded films, the mixed micelles integrated into the sublingual films delivered noticeably superior outcomes[34]. It was discovered that the concentrations of PVP had a significant impact on the appearance of film and mechanical strength. Based on its acceptable mechanical strength and quick disintegration characteristics, PVP was chosen as the film-forming material. Above their CMC, the mixed micelles of TPGS and poloxamer-188 developed. The findings suggested that the requisite entrapment efficiency and particle size were successfully prepared in the micelles-integrated sublingual films. The F-5 had the perfect characteristics for the delivery of curcumin micelles via sublingual routes.

## 5. Conclusions

Poloxamer-188 and TPGS-1000 micelles with curcumin have been successfully loaded onto sublingual films. The ideal values for thickness, weight, surface pH, and disintegration time were produced by the prepared sublingual film formulation (F-5). The prepared films with micelles for sublingual can be used to increase the solubility of curcumin due to their enormous surface area, decreased particle size, and transformation of curcumin into an amorphous form. *In vitro* tests revealed that TPGS-1000 and poloxamer-188 had good permeability and rapid absorption. Consequently, the curcumin-loaded micelles in sublingual films greatly increase curcumin's bioavailability and may be a different way to deliver medications that are not very soluble.

## 6. References


1. Srimal RC. Turmeric: A brief review of medicinal properties. Fitoterapia (Milano). 1997; 68(6):483-9.
2. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: A short review. Life Sciences. 2006; 78(18):2081-7. https://doi.org/10.1016/j.lfs.2005.12.007
3. Duvoix A, Blasius R, Delhalle S, Schnekenburger M, Morceau F, Henry E, Dicato M, Diederich M. Chemopreventive and therapeutic effects of curcumin. Cancer Letters. 2005; 223(2):181-90. https://doi.org/10.1016/j.canlet.2004.09.041
4. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Research. 2003; 23(1/A):363-98.
5. Wang Z, Zhang Y, Banerjee S, Li Y, Sarkar FH. Retracted: Notch–1 down–regulation by curcumin is associated with the inhibition of cell growth and the induction of apoptosis in pancreatic cancer cells. Cancer. 2006; 106(11):2503-13. https://doi.org/10.1002/cncr.21904
6. Lev-Ari S, Strier L, Kazanov D, Madar-Shapiro L, Dvory-Sobol H, Pinchuk I, Marian B, Lichtenberg D, Arber N. Celecoxib and curcumin synergistically inhibit the growth of colorectal cancer cells. Clinical Cancer Research. 2005; 11(18):6738-44. https://doi.org/10.1158/1078-0432.CCR-05-0171
7. Cruz–Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, Giardiello FM. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clinical Gastroenterology and Hepatology. 2006; 4(8):1035-8. https://doi.org/10.1016/j.cgh.2006.03.020
8. Wang YJ, Pan MH, Cheng AL, Lin LI, Ho YS, Hsieh CY, Lin JK. Stability of curcumin in buffer solutions and characterization of its degradation products. Journal of Pharmaceutical and Biomedical Analysis. 1997; 15(12):1867-76. https://doi.org/10.1016/S0731-7085(96)02024-9
9. Cheng AL, Hsu CH, Lin JK, Hsu MM, *et al.* "Phase I chemoprevention clinical trial of curcumin, a chemo preventive agent, in patients with high risk or pre-malignant lesions". Anticancer Research. 2001; 21(4):2895-2900.
10. Kazunori Kataoka, Atsushi Harada, Yukio Nagasaki. "Block copolymer micelles for drug delivery: design, characterization and biological significance". Advanced Drug Delivery Reviews. 2012; 64:37-48. https://doi.org/10.1016/j.addr.2012.09.013
11. Bromberg L. Polymeric micelles in oral chemotherapy. Journal of Controlled Release. 2008; 128(2):99-112. https://doi.org/10.1016/j.jconrel.2008.01.018
12. Attia AB, Ong ZY, Hedrick JL, Lee PP, Ee PL, Hammond PT, Yang YY. Mixed micelles self-assembled from block copolymers for drug delivery. Current Opinion in Colloid and Interface Science. 2011; 16(3):182-94. https://doi.org/10.1016/j.cocis.2010.10.003
13. Ma X, Williams RO. Polymeric nanomedicines for poorly soluble drugs in oral delivery systems: An update. Journal of Pharmaceutical Investigation. 2018; 48(1):61-75.
14. Lv QY, Li XY, Shen BD, Dai L, Xu H, Shen CY, Yuan HL, Han J. A solid phospholipid-bile salts-mixed micelles based on the fast-dissolving oral films to improve the oral bioavailability of poorly water-soluble drugs. Journal of Nanoparticle Research. 2014; 16(6):1-4. https://doi.org/10.1007/s11051-014-2455-6
15. Guo YG, Singh AP. Emerging strategies for enhancing buccal and sublingual administration of nutraceuticals and pharmaceuticals. Journal of Drug Delivery Science and Technology. 2019; 52:440-51. https://doi.org/10.1016/j.jddst.2019.05.014
16. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Frontiers in Pharmacology. 2019; 10:1328. https://doi.org/10.3389/fphar.2019.01328
17. Kaldybekov DB, Tonglairoum P, Opanasopit P, Khutoryanskiy VV. Mucoadhesive maleimide-functionalised liposomes for drug delivery to urinary bladder. European Journal of Pharmaceutical Sciences. 2018; 111:83-90. https://doi.org/10.1016/j.ejps.2017.09.039
18. Ahn H, Park JH. Liposomal delivery systems for intestinal lymphatic drug transport. Biomaterials Research. 2016; 20(1):1-6. https://doi.org/10.1186/s40824-016-0083-1
19. Chunhachaichana C, Srichana T. Efficiency of sildenafil encapsulation in poloxamer micelles. Journal of Dispersion Science and Technology. 2019; 40(10):1461-8. https://doi.org/10.1080/01932691.2018.1518142

20. Wang T, Markham A, Thomas SJ, Wang N, Huang L, Clemens M, Rajagopalan N. Solution stability of poloxamer 188 under stress conditions. Journal of pharmaceutical sciences. 2019; 108(3):1264-71. https://doi.org/10.1016/j.xphs.2018.10.057
21. Tambe A, Pandita N. Enhanced solubility and drug release profile of boswellic acid using a poloxamer-based solid dispersion technique. Journal of Drug Delivery Science and Technology. 2018; 44:172-80. https://doi.org/10.1016/j.jddst.2017.11.025
22. Joseph G. Moloughney, Noah Weisleder. Poloxamer 188 (p188) as a membrane resealing reagent in biomedical applications. Recent Patents on Biotechnology. 2012; 6(3):200-11. https://doi.org/10.2174/1872208311206030200
23. Singh-Joy SD, McLain VC. Safety assessment of poloxamers 101, 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403, and 407, poloxamer 105 benzoate, and poloxamer 182 dibenzoate as used in cosmetics. International Journal of Toxicology. 2008; 27:93-128. https://doi.org/10.1080/10915810802244595
24. Hu XY, Lou H, Hageman MJ. Preparation of lapatinib ditosylate solid dispersions using solvent rotary evaporation and hot melt extrusion for solubility and dissolution enhancement. International Journal of Pharmaceutics. 2018; 552(1-2):154-63. https://doi.org/10.1016/j.ijpharm.2018.09.062
25. Kim DS, Kim DW, Kim KS, Choi JS, Seo YG, Youn YS, Oh KT, Yong CS, Kim JO, Jin SG, Choi HG. Development of a novel l-sulpiride-loaded quaternary microcapsule: Effect of TPGS as an absorption enhancer on physicochemical characterization and oral bioavailability. Colloids and Surfaces B: Biointerfaces. 2016; 147:250-7. https://doi.org/10.1016/j.colsurfb.2016.08.010
26. Singh H, Narang JK, Singla YP, Narang RS, Mishra V. TPGS stabilized sublingual films of frovatriptan for the management of menstrual migraine: Formulation, design and antioxidant activity. Journal of Drug Delivery Science and Technology. 2017; 41:144-56. https://doi.org/10.1016/j.jddst.2017.07.008
27. Keshari P, Sonar Y, Mahajan H. Curcumin loaded TPGS micelles for nose to brain drug delivery: *in vitro* and *in vivo* studies. Materials Technology. 2019; 34(7):423-32. https://doi.org/10.1080/10667857.2019.1575535
28. Jain S, Pandey S, Sola P, Pathan H, Patil R, Ray D, Aswal VK, Bahadur P, Tiwari S. Solubilization of carbamazepine in TPGS micelles: Effect of temperature and electrolyte addition. Aaps Pharm SciTech. 2019; 20(5):1-8. https://doi.org/10.1208/s12249-019-1412-1
29. Suksiriworapong J, Rungvimolsin T, Junyaprasert VB, Chantasart D. Development and characterization of lyophilized diazepam-loaded polymeric micelles. Aaps Pharm SciTech. 2014; 15(1):52-64. https://doi.org/10.1208/s12249-013-0032-4
30. Dai WG, Dong LC, Li S, Deng Z. Combination of Pluronic/Vitamin E TPGS as a potential inhibitor of drug precipitation. International Journal of Pharmaceutics. 2008; 355(1-2):31-7. https://doi.org/10.1016/j.ijpharm.2007.12.015
31. Nasirizadeh S, Malaekeh-Nikouei B. Solid lipid nanoparticles and nanostructured lipid carriers in oral cancer drug delivery. Journal of Drug Delivery Science and Technology. 2020; 55:101458. https://doi.org/10.1016/j.jddst.2019.101458
32. Carn SA, Fioletov VE, McLinden CA, Li C, Krotkov NA. A decade of global volcanic SO2 emissions measured from space. Scientific Reports. 2017; 7(1):1-2. https://doi.org/10.1038/srep44095
33. Lim SJ, Kim CK. Formulation parameters determining the physicochemical characteristics of solid lipid nanoparticles loaded with all-trans retinoic acid. International Journal of Pharmaceutics. 2002; 243(1-2):135-46. https://doi.org/10.1016/S0378-5173(02)00269-7
34. Shen CY, Yuan XD, Bai JX, Lv QY, Xu H, Dai L, Yu C, Han J, Yuan HL. Development and characterization of an orodispersible film containing drug nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics. 2013; 85(3):1348-56. https://doi.org/10.1016/j.ejpb.2013.09.019
35. Panda DS, Alruwaili NK, Pattnaik S, Swain K. Ibuprofen loaded electrospun polymeric nanofibers: A strategy to improve oral absorption. Acta Chimica Slovenica. 2022; 69(2):483-8. https://doi.org/10.17344/acsi.2022.737
36. Sumitha CH, Varma MV, Sriniwas K. Development of taste masked fast dissolving orally consumable films of seldinafil citrate. IJPIS J Pharm Cosmet 2011; 1:1-6.
37. Navamanisubramanian R, Nerella R, Chamundeeswari D,Shanmuganathan S. Use of okra mucilage and chitosan acetate in verapamil hydrochloride buccal patches development; *in vitro* and ex vivo characterization. J Young Pharm 2017; 9:94-9.