https://doi.org/10.33472/AFJBS.6.Si2.2024.3583-3595

Chitosan -Xanthan Gum Polyelectrolyte Complex Gel Containing Curcumin Loaded Porous Silica For Wound Healing

Harita Desai[1*], Yashashree Salunkhe[1], Gauri Lokhande[1], Shubhangi Sonawane[2], Vinod Mule[3,4], Sachin Kadam[5]

[1]Department of Pharmaceutics, Bombay College of Pharmacy, Mathuradas Colony, Santacruz East, Mumbai-400 098, India.

[2]Department of Pharmaceutical science, Prof. Ravindra Nikam College of Pharmacy, Gondur, Tal. Dist. Dhule, 424002.

[3]Department of Pharmacology, Bombay Institute of Pharmacy and Research, Dombivali, Maharashtra, 421201.

[4]Department of Pharmacology, Yashwantrao Bhonsale College of Pharmacy, Sawantwadi, Maharashtra, 416510.

[5]Department of Chemistry, Vishal Institute of Pharmaceutical Education and Research, Ale, Tal. Junnar, Pune, Maharashtra, 412411.

***Corresponding author:**
Dr. Harita Desai,
Assistant Professor,
Department of Pharmaceutics,
Bombay College of Pharmacy, Mathuradas Colony, Santacruz East, Mumbai -400 098, India
Email id: harita.desai@bcp.edu.in

ABSTRACT

Curcumin, a BCS Class IV drug exhibiting poor solubility possesses its wound healing property owing to its anti-inflammatory, antioxidant and anti-infectious activities. The objective of the current study was to load Curcumin on porous silica Aeroperl ® 300 Pharma for solubility enhancement. The Curcumin loaded silica was further incorporated into a Chitosan-Xanthan gum polyelectrolyte complex gel with final application for wound healing activity. Curcumin was loaded on Aeroperl® 300 Pharma in 3 ratios of 1:1, 1:2 and 1:5 and the Curcumin loaded silica was evaluated for solubility, drug contentand in vitro drug release in Phosphate buffered saline PBS pH 7.4. Curcumin loaded silica in ratio 1:5 was found to show highest solubility of 0.68±0.02 µg/ml in PBS pH 7.4 and drug content of 88.3±0.17% and in vitro drug release 1.48 times higher than plain Curcumin. The Chitosan Xanthan gum polyelectrolyte complex based gel containing Curcumin loaded silica when evaluated was found to show desirable pH of

6.67, particle size of 260.6 ± 1.25 nm, in vitro release similar to drug loaded silica in ratio 1:5and high anti-infective wound healing efficacy against *Pseudomonas denitrificans.*
KEYWORDS: Chitosan, Xanthan gum, polyelectrolyte complex, Curcumin, wound healing, silica

INTRODUCTION:

Poor solubility of New chemical entities has posed a serious challenge in designing suitable bioavailable dosage forms. About 40% of New chemical entities face problems in commercialization owing to poor solubility [1,2]. The issue of poor solubility of drug has been addressed by several physical and chemical meansout of which drug amorphization is the most promising technique.[3] Amorphous drugs exhibit high free energy state and a higher molecular mobility as compared to crystalline compounds which exist with an ordered structure. [4,5]. The higher free energy and mobility aids to enhance the solubility and dissolution rate thus ultimately enhancing the bioavailability of the compound. Drug loading on porous carrier materials like silica has been widely attempted technique for amorphization thus leading to enhanced solubility and bioavailability of drug. The extent to which drug loading aids to enhance solubility depends on the nature of porous carrier, the concentration of drug and the method of drug loading [6]. Drug loading on silica is advantageous owing to the presence of larger number of pores on the silica which makes the existence of the drug inside the pore to be in a disordered state, a more thermodynamically favourable process without creating issues of recrystallization and instability [7]. Silica has been widely studied in drug delivery in solubility enhancement by formulation of solid dispersions using silicas like Aeroperl® 300 Pharma. [8,9]

Skin provides barrier activity against environment and shows several protective functions. Acute or chronic injuries lead to compromise in the skin integrity. This leads to initiation of a multistep dynamic process by the body which leads to tissue healing and restoration of barrier properties of the skin. Wound healing comprises of four stages namely haemostasis, inflammation, proliferation and remodelling. Curcumin has been studied to be a promising herbal agent in wound healing. Curcumin is present as one of the three curcuminoids present in Turmeric plant Curcumin is a BCS Class IV drug exhibiting poor solubility and poor bioavailability [10]. It exhibits poor absorption, stability and bioavailability issues. Owing to its lipophilic nature, it shows limited transmembrane permeability. Curcumin exhibits its wound healing property owing to its anti-inflammatory, antioxidant and anti-infectious activities.[11] It increases cutaneous wound healing by its role in tissue remodelling, collagen deposition, granulation tissue formation etc. It increases epithelial regeneration and fibroblast

proliferation. It reduces oxidation which is a major cause of inflammation. It accelerates wound healing by enhancing the wound contraction rate. [12,13]. Topical application of larger doses of Curcumin are found to induce topical toxicity.

Polyelectrolyte complex networks are results of self-assembly and association owing to formation of strong reversible electrostatic linkage by mixing of oppositely charged polyelectrolytes in solution. [14] These polyelectrolyte networks result in biocompatible hydrogels which are very well tolerated and sensitive to environmental factors. Polyelectrolyte complexes may be stoichiometric or non-stoichiometric in nature. Stoichiometric polyelectrolyte complexes form precipitates whereas non-stoichiometric ones are soluble. Some of the parameters that determine the successful formation and stability of polyelectrolyte complexes include density of charges on polyelectrolytes, the mixing order and ratio, the nature of the ionic groups, the order of addition, the intensity of interaction etc. [15,16]

Chitosan comprises of deacetylated polymer derivative of chitin, a natural polysaccharide. Chitosan is available in different degree of deacetylation and molecular weights. It comprises of β-1,4-linked glucosamine and N-Acetyl-D-glucosamine which are present at varying degree of deacetylation between 70-95 % and with molecular weights varying between 10-1000 kDa. It has been extensively studied as a carrier material for drug delivery systems. Xanthan Gum chemically is an exopolysaccharide consisting of cellulosic backbone comprising of ®-(1,4)-D-glucopyranose glucan, with a (3,1)-⟨-D-mannopyranose-(2,1)-®-D-glucuronic acid-(4,1)-®-D-mannopyranose, on every second glucose residue. Chitosan has cationic amino groups on the C2 position of repeating glucopyranose units which show the ability to electrostatically interact with anionic groups of polyanions like Xanthan Gum. The interaction leads to coacervation leading to formation of a hydrogel with a quasi-ordered network. The hydrogel exhibits a structural modification after mixing leading to formation of a solid-state compound. Chitosan-xanthan gum polyelectrolyte complexes form a matrix that shows a unique application of dissolution enhancement of poorly-water soluble drugs. [17-20]

The objective of the present study was to modulate the solubility and dissolution profile of Curcumin byloading it on silica and further encapsulatingit in polyelectrolytecomplex gel comprising of Chitosan and Xanthan gum. The Curcumin loaded silica was evaluated for solubility, drug content, and in vitro drug release .and the polyelectrolyte complex gel containing Curcumin loaded silica was evaluated for pH, particle size, Scanning electron microscopy, viscosity, and in vitro release Further the polyelectrolyte complex gel containing Curcumin loaded silica was evaluated for anti-infective potential in wound healing.

MATERIALSAND METHODS

Curcumin was gifted by K. Patel Phyto extractions Pvt Ltd (Gujrat). Aeroperl ®300 Pharma was obtained as a gift sample from Evonik Industries, Mumbai, India. Sodium hydroxide, Sodium chloride, Sodium bicarbonate, Calcium chloride dihydrate, methanol waspurchased from S.D. Fine-Chem, Limited, Mumbai, India. All other chemicals and solvents used were of analytical grade.

Drug loadingon Aeroperl® 300 Pharma

Drug loaded silica -Aeroperl® 300 Pharma was formulated by wetness impregnation method.A solution of Curcumin in acetone was prepared by adding Curcumin in 5ml of acetone and the solution was stirred. Aeroperl® 300 Pharma was added to the drug solution inthe ratios of 1:1, 1:2, and 1:5 of drug: silica.The solvent from the clear solution was allowed to evaporate by covering the solution with aluminium foil and piercing 5–6 little holes in the foil. The evaporation was conducted at room temperature with continuous stirring. The process was continued till the final product was obtained.[21]

Formulation of polyelectrolyte complex gel:

Ionic gelation method was used to prepare polyelectrolyte complex gel using chitosan and xanthan gum.Solution A was made up of a cationic Chitosan solution comprising of 3 mg/ml of Chitosan in a 1% (v/v) acetic acid solution with a pH of 3.5. 0.5 mg/ml anionic solution of xanthan gum was prepared in distilled water and marked as B. Solution B was added to solution A with magnetic stirring at constant 800 rpmat 250 °C temperature. This mixture was continuously stirred for additional 10 minutes for the completion of ionic gelation process to create the complex. [22]

Incorporation of drug loaded silica into polyelectrolyte complex gel

5mg of drug loaded silica powder was added into the polyelectrolytedispersion under magneticstirring. This solution was kept under constant stirring for 15 minutes in order to get finalpolyelectrolyte dispersion.

Characterization of drug loaded silica system:

Solubility studies of drug loaded silica system:

Saturation solubility was measured by using the standardised water bath shaker method maintaining the sample at 37°C with a 20-rpm speed for 48 hours. The apparent solubility was evaluated in deionized water and phosphate buffer pH 7.4. For the solubility study, an excessive amount of CUR and CUR-loaded silica sample (ratio 1:2, 1:3, 1:5) were dispersed in 10 ml of deionized water and phosphate buffer pH7.4. Samples were filtered through 0.2μm membrane

filters after shaking for 48 hours, and the filtrate was then properly diluted with the medium used for solubility testing. The measurement was conducted using UV-visible spectrophotometer (Shimadzu UV-9000) at wavelength of 422 nm.[23]

Drug Content of drug loaded silica system

10 mg of the material was precisely weighed and dissolved in 10 ml of glacial acetic acid (AR). The sample solution was sonicated for 10 minutes and was centrifuged at 10,000 rpm for 5 minutes. An appropriate amount of methanol was added to the supernatant to dilute it. Using a UV-Visible Spectrophotometer, the absorbance was measured at 422 nm. By plotting an absorbance versus concentration standard curve, the drug content was calculated.

Studies on Optimised Drug: Silica System

In-vitro release study of drug loaded silica system

The dialysis bag method was used to conduct release study for drug solution and drug-loaded silica systems. The dialysis bags (Dialysis Membrane- 50Av. Flat-24.26 mm, Av. diameter-14.3 mm, capacity approximately-1.61 ml/cm) are soaked in filtered, distilled water for an entire night in order to open the pores and permit the passage of solute molecules through the dialysis membrane. In the dialysis bag, 1mg/mL of the drug solution and prepared drug-loaded silica powder were placed, and the bags were tied at both ends with strings. These bags were then gently shaken on a magnetic stirrer while being immersed in 50 ml of PBS pH 7.4 as a release medium, at 37± 0.5 °C. at 0, 5, 10, 15, 30, and 45 minutes, and 1, 2, 4, 6, and 8 and 10 hours, 1ml aliquots were withdrawn from the release medium and replaced with 1ml of new release media. Then the samples were analysed using UV –visible spectroscopy and the cumulative release was computed. For each sample, the tests were run in triplicate.[24]

Characterization of PEC gelling system

Appearance and pH measurement-

The optimized topical gel formulation was examined for appearance, colour, texture and odourqualitatively. The gel was analysed for pH using pH meter.

Particle size and Polydispersity index (PDI)

After measuring and transferring 0.1g of gel into an Eppendorf, 1ml of filtered, distilled water was added. This system was allowed to stand for 30 min. Particle size and polydispersity index was measured using Malvern ZS UK at room temperature.[25]

Scanning Electron Microscopy (SEM)

Scanning electron microscopy is used to characterize the size, shape, and surface morphology of sample by scanning them with a high-energy electron beam in a raster scan pattern. To eliminate remaining moisture, samples are put on a piece of carbon fibre and kept in a

desiccator. After that, the sample is sputtered with a thin coating of gold to reduce charge and increase picture quality. The sample's atoms and electrons interact to produce a variety of signals, each of which contains details on the sample's surface topography and chemical composition.[26]

Viscosity

The Viscosity of gel was measured by using a Brookfield viscometer.250 mg of developed formulation was placed onto theplate below the cone spindle and solvent trap. Thetemperature control was set to temperature 25°C. The temperature of cone was allowed to equilibratewith the plate for 10 mins. The spindle was rotatedin the formulation at shear rates of 20, 30, 40, 60and 80 rpm and corresponding dial readings onthe viscometer were noted so as to obtain an up curve. The visosity of the gel was determined using factor.

***In-vitro* release study**

In-vitro release study for gel was carried using dialysis bag method. In this method, dialysis bags (Dialysis Membrane- 50Av.flat-24.26 mm, Av. diameter- 14.3 mm, capacity approx.-1.61 ml/cm) were soaked overnight in filtered distilled water in order to open the pores and to allow movement of solute molecules across the dialysis membrane. 1mg/mL of the drug solution and prepared formulations were taken in the dialysis bag and the bags were secured at both ends by means of strings. These bags were then dipped in 50 ml of PBS pH 7.4 as a release medium, at 37 ± 0.5°C and provided with gentle shaking on the magnetic stirrer. 1ml aliquots were withdrawn from the release medium at 0, 5, 10, 15, 30, 45 minutes and after 1, 2, 4, 6, 8 and 10 hours and were replaced with 1ml of fresh release medium. These aliquots were then analysed by UV Spectroscopy at 422nm and its cumulative release was calculated. Plot of cumulative release versus time were used to determine the release of drug from the formulation. The studies were performed in triplicate for each sample.[27]

Antimicrobial assay

The antimicrobial assay of Curcumin was performed by comparing the zone of inhibition. To conduct the microbiological assay, a cup and plate method was used.The zone of inhibition is generated around the cylinder cavity using this technique, which involves diffusion of antibiotic from the cylindrical cavity to the agar layer containing microorganism.The main objective of this experiment was to evaluate the antimicrobial efficacy of the optimized formulations using *Pseudomonas denitrificans* and compare with standard using cup-plate method[28]

Pseudomonas D. was grown on agar at 30℃-35℃ for 18- 24 hrs. Growth was suspended in standard saline and culture density was adjusted. Suggested inoculum composition

1.0ml/100ml medium.20 ml media and 0.2 ml of culture suspension were poured in a sterile petri plate and allowed it to solidify. A well was bored in the plate with cork borer of 8mm diameter. 100 µl of sample was filled as such in a well. The test was carried out in duplicate. The plates were incubated at 30℃ to 35℃ for 18-24 hrs. Diameter of zone of inhibition was measured and reading were taken in triplicate.

RESULT AND DISCUSSION

Solubility studies of drug loaded silica system:

The solubility of Curcumin was found to increase with the concentration of silica in the order of 1:2, 1:3 and 1:5 respectively when measured in water and Phosphate buffered saline pH 7.4.respectively.(Table 1) The ratio having highest concentration of silica ie 1:5 was found to show highest solubility of Curcumin in water and PBS pH 7.4 The previously existing crystalline Curcumin transforms into molecular dispersed Curcumin which gets entrapped in the pores of porous silica and exists in amorphous form thus enhancing the solubility of Curcumin. [29]

Table 1. Solubility of Curcumin loaded silica in 3 ratios in water and PBS pH 7.4

Ratio (Drug: Silica)	Solubility in water (mg/ml)	Solubility in PBS pH7.4 (mg/ml)
1:2	0.18±0.01	0.38±0.04
1:3	0.20±0.05	0.45±0.01
1:5	0.24±0.03	0.68±0.02

Drug Content of drug loaded silica system:

By employing a standard curve plotted as an absorbance versus concentration plot, the amount of drugwas calculated. Curcumin loaded on silica in ratio of 1:5 was found to show highest drug content of 88.3% .(Table 2)

Table 2. Drug content of Curcumin loaded silica in 3 ratios

Ratio (Drug: Silica)	Drug Content (%)
1:2	75.4±0.24
1:3	82±0.31
1:5	88.3±0.17

Based on the solubility data, the drug:silica ratio of 1:5 was found to be most optimised and considered for further studies.

Studies on Optimised Drug loaded Silica system

***In-vitro* drug release study:**

The drug loaded silica system in ratio of 1:5 of Curcumin to Aeroperl ® 300 Pharma was found to show a 1.48 times enhancement in release of drug when compared to Curcumin solution (Figure 1).

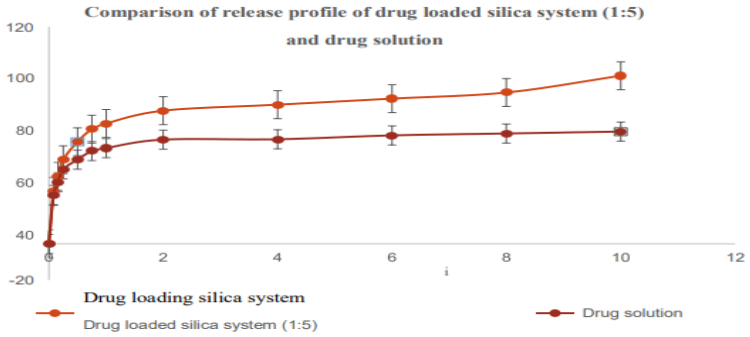

Figure 1. In vitro release profile of Curcumin solution and Curcumin loaded silica in 1:5

Characterization of polyelectrolyte complex gel

Appearance and pH measurement

The curcumin-loaded silica in the PEC gel was uniform and appeared faintly yellow.(Figure 2)

Figure 2: Curcumin loaded Chitosan-Xanthan gum polyelectrolyte complex gel

The xanthan gum-containing gel pH was determined to be 6.67, indicating that the gel is suitable for topical application.The pH of the polyelectrolytes play a very important role in success of polyelectrolyte complexation.The extent to which Chitosan protonates and Xanthan gum anionises depends on the pH of the solution**.** The cross linking density of the polyelectrolyte complexes depends on the pH of chitosan solution.

Particle size and Polydispersity index (PDI)

The particle size and polydispersity index of the blank PEC gel formulation and the curcumin-loaded PEC gel formulation were found to be 179.8 ± 0.56 nm, 0.282 ± 0.015 nm and 260.6 ± 1.25 nm, 0.318 ± 0.02 nm respectively. Curcumin loading on the PEC gel was found to enhance the particle size of blank PEC gel.

Scanning Electron Microscopy (SEM)

Curcumin was found to show a flat, rod-like structure whereas Curcumin loaded PEC gel was found to show broken spherical porous morphology. (Figure 3)

Figure 3. SEM Image of Curcumin and Curcumin loaded Polyelectrolyte complex gel

.Viscosity

Viscosity of the PEC gel measured by Brookfield viscometer was found to be 153 cPs. The viscosity values higher than plain Chitosan and Xanthan gum indicated successful formation of gel suitable for topical application. The extent to which the cationic polyelectrolyte interacts with anionic polyelectrolyte is dependent on the viscosity of the individual solutions. The viscosity of the solution determines the architecture of polymeric chain and the distribution of charge of the polymeric chain available for electrostatic interaction.

***In-vitro* release study**

The invitro release profile of Curcumin from PEC gel was found to be 1.43 times higher to plain drug solution. The encapsulation of drug loaded silica in PEC gel was found to show comparable drug release as compared to drug loaded silica. (Figure 4)

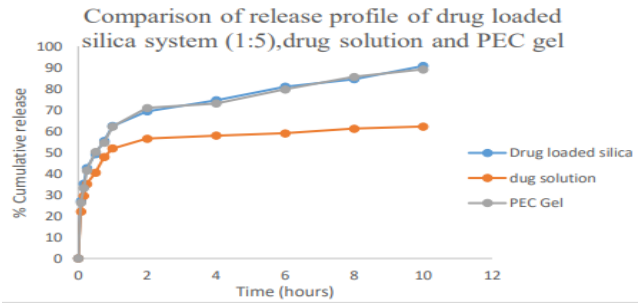

Figure 4. Comparative in vitro release profile of Curcumin solution, Curcumin loaded silica 1:5, and Polyelectrolyte complex gel containing Curcumin loaded silica 1:5

Antimicrobial Assay:

Distinct zone of inhibition was observed in the petri plate containing dispersion of the drug loaded silica and PEC gel. Petri plate with 0.9% saline did not show any zone of inhibition whereas in the petri plate containing the drug-loaded silicaand PEC gel, higher zone of inhibitions wereobservedi.e. 31.18 mm and 34.88 mms (Figure 5). These zone of inhibitions

was found to be greater than the standard value of 18 thus indicating higher antibacterial efficacy of Curcumin against *Pseudomonosdenitrificans* from drug loaded silica and Polyelectrolyte gel. Thus the Chitosan Xanthan gum polyelectrolyte complex gel containing Curcumin loaded Aeroperl ® 300 Pharma was found to show antiinfective potential against *Pseudomonas denitrificans* which is infectious agent in wound formation.

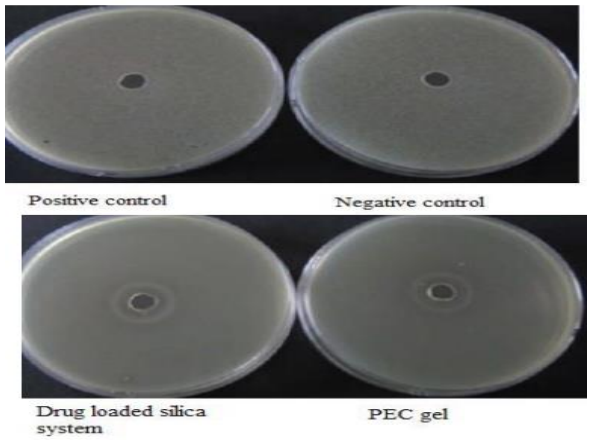

Figure 5. Zone of inhibition of saline, positive control, Curcumin loaded silica system and PEC gel containing Curcumin loaded silica

CONCLUSION

Curcumin was successfully loaded on Aeroperl®300 Pharma. The drug loading on porous silica was found to enhance the drug release in Phosphate buffered saline pH 7.4 by 1.48 times as compared to plain Curcumin. A polyelectrolyte complex gel was successfully formulated using Chitosan and Xanthan gum. The polyelectrolyte gel was found to show drug release comparable to drug loaded silicaAeroperl ® 300 Pharma . Both the Curcumin loaded silica and the Polyelectrolyte complex gel containing drug loaded silica were found to show enhanced antibacterial efficacy of Curcumin against *Pseudomonas dentrificans*. Thus drug loading on silica can be considered as a prospective strategy for solubility enhancement. Chitosan Xanthan gum Polyelectrolyte complex based gels as suitable carrier systems for Curcumin loaded silica with enhanced Curcumin solubility and permeation can be considered as promising systems for Wound healing.

ACKNOWLEDGEMENTS

The authors are thankful to K Patel Phytoextracts, Gujarat, India for providing gift sample of Curcumin and to Evonik Degussa, Mumbai, India for providing with gift sample of Aeroperl ® 300 Pharma. The authors are thankful to Bombay College of Pharmacy-Autonomous for providing infrastructural facilities for conducting research work.

REFERENCES

1] Friesen, DT. Shanker, R. Crew, M. Smithey, D. T. Curatolo, W.J. and Nightingale JAS (2008). Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. *Mol Pharm*. 5(6), 1003–1019.

2) Al-Hamidi, H. Edwards, AA. Mohammad, M.A.and Nokhodchi, A. (2010). To enhance dissolution rate of poorly water-soluble drugs: glucosamine hydrochloride as a potential carrier in solid dispersion formulations. *Colloids Surf B Biointerfaces*. 76(1), 170–178.

3) Kim, D.H. Kim, Y.W. Tin, Y.Y. Soe, M.T. Ko, B.H. Park, S.J.and Lee,J.W.(2021). Recent Technologies for Amorphization of Poorly Water-Soluble Drugs. *Pharmaceutics.* 23;13(8), 1318. https://doi: 10.3390/pharmaceutics13081318.

4) Edueng, K.Mahlin, D. Grasjo, J.Nylander, O.Thakrani, M. and Bergstrom, CAS. (2019). Supersaturation Potential of Amorphous Active Pharmaceutical Ingredients after Long-Term Storage. *Molecules*.24(15), 2731.https://doi: 10.3390/molecules24152731.

5) Porrang, S.Davaran, S.Rahemi, N.Allahyari, S.and Mostafavi,E.(2022). How Advancing are Mesoporous Silica Nanoparticles? A Comprehensive Review of the Literature. *Int J Nanomedicine.*22;17,1803-1827.https://doi: 10.2147/IJN.S353349.

6) Jafari, S.Derakhshankhah, H. Alaei, L. Fattahi, A.Varnamkhasti, BS. andSaboury, A.A. (2019). Mesoporous silica nanoparticles for therapeutic/diagnostic applications. *Biomed Pharmacother.* 109:1100-1111. https://doi: 10.1016/j.biopha.2018.10.167.

7) Trzeciak, K.Chotera-Ouda, A. Bak-Sypien II, Potrzebowski, MJ. (2021). Mesoporous Silica Particles as Drug Delivery Systems-The State of the Art in Loading Methods and the Recent Progress in Analytical Techniques for Monitoring These Processes. Pharmaceutics. 24;13(7), 950.https://doi: 10.3390/pharmaceutics13070950.

8)S, Sethia. E, Squillante.(2004). Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods, International Journal of *Pharmaceutics*,272,1–2, 1-10,

9) Meer, T. Fule, R. Khanna, D. and Amin,P.(2013) Solubility modulation of bicalutamide using porous silica. *Journal of Pharmaceutical Investigation* **43**, 279–285 https://doi.org/10.1007/s40005-013-0070-7

10) Kumari, A. Raina, N. Wahi, A. Goh, K.W. Sharma, P. Nagpal, R. Jain, A.Ming, L.C.and Gupta, M.(2022). Wound-Healing Effects of Curcumin and Its Nanoformulations: A Comprehensive Review. Pharmaceutics 14, 2288. https://doi.org/10.3390/ pharmaceutics14112288

11) Mohanty, C. Sahoo, S.K.(2017). Curcumin and Its Topical Formulations for Wound Healing Applications. *Drug Discov*. Today 22, 1582–1592.

12) Akbik D. Ghadiri, M. Chrzanowski, W. and Rohanizadeh, R. (2014). Curcumin as a wound healing agent, *Life Sci*. 116(1):1-7.http://dx.doi.org/10.1016/j.lfs.2014.08.016

13) Joe, B. Vijaykumar, M. Lokesh, B.(2004). Biological properties of curcumin-cellular and molecular 586 mechanisms of action. *Crit Rev Food Sci Nutr*. 44:97–111

14) Ilina, A.V. Varlamov, V.P.(2005). Chitosan-based polyelectrolyte complexes: A review. *Appl. Biochem. Microbiol*. 41, 5–11.

15) Wanasingha, N. Dorishetty, P. Dutta, N.K. and Choudhury, N.R.(2021). Polyelectrolyte Gels: Fundamentals, Fabrication and Applications. *Gels* 7, 148. https://doi.org/ 10.3390/gels7030148

16) Etrych, T. Leclercq, L. Boustta, M.and Vert, M. (2005). Polyelectrolyte complex formation and stability when mixing polyanions and polycations in salted media: A model study related to the case of body fluids. *Eur. J. Pharm. Sci.* 2, 281–288

17) Hamman, JH. (2010). Chitosan based polyelectrolyte complexes as potential carrier materials in drug delivery systems. *Mar Drugs.* 8(4):1305-22. https://doi: 10.3390/md8041305.

18) Ciric, A.Medarevic, D. Calija, B.Dobricic, V.Mitric, M. and Djekic, L.(2020) Study of chitosan/xanthan gum polyelectrolyte complexes formation, solid state and influence on ibuprofen release kinetics. *Int J Biol Macromol*.148:942-955. https://doi: 10.1016/j.ijbiomac.2020.01.138.

19) Luo, Y. Wang,Q.(2014). Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery. *Int J BiolMacromol*. 64, 353-67. https://doi: 10.1016/j.ijbiomac.2013.12.017.

20) Tsai, R.Y. Chen, P.W. Kuo, T.Y. Lin, C.M. Wang, D.M. Hsien, T.Y.and Hsieh, HJ. (2014). Chitosan/pectin/gum Arabic polyelectrolyte complex: process-dependent appearance, microstructure analysis and its application. *CarbohydrPolym*. 2014. 101:752-9. https://doi: 10.1016/j.carbpol.2013.10.008.

21)Pawar, J. Desai, H.Moravkar, K. Khanna, D. and Amin, P. (2016). Exploring the potential of porous silicas as a carrier system for dissolution rate enhancement of artemether.*Asian journal of pharmaceutical sciences* 11, 760–770

22)Argin-Soysal, S. Kofinas, P. and Lo, Y.M.(2009). Effect of complexation conditions on xanthan-chitosan polyelectrolyte complex gels. *Food Hydrocol*. 23, 202–209

23) Ibrahim, A.H.Smatt, J.H.Govardhanam, N.P. Ibrahim, H.M. Ismael, H.R.Afouna, M.I. Samy, A.M. and Rosenholm, J.M.(2020). Formulation and optimization of drug-loaded mesoporous silica nanoparticle-based tablets to improve the dissolution rate of the poorly water-soluble drug silymarin. *Eur J Pharm Sci*. 2020. 142:105103. https://doi: 10.1016/j.ejps.2019.105103.

24)Velho, M.C. Funk, N.L. Deon, M. Benvenutti, E.V. Buchner, S. Hinrichs, R. Pilger, D.A. and Beck, R.C.R.(2024) Ivermectin-Loaded Mesoporous Silica and Polymeric Nanocapsules: Impact on Drug Loading, In Vitro Solubility Enhancement, and Release Performance. *Pharmaceutics.* 16(3):325. https://doi: 10.3390/pharmaceutics16030325.

25) Din, F.U. Jin, S.G.and Choi, H. G.(2021) Particle and Gel Characterization of Irinotecan-Loaded Double-Reverse Thermosensitive Hydrogel. *Polymers.*13(4):551. https://doi: 10.3390/polym13040551.

26) Bernardi, S. Bianchi, S. Tomei, A.R. Continenza, M.A.and Macchiarelli,G.(2019). Microbiological and SEM-EDS Evaluation of Titanium Surfaces Exposed to Periodontal Gel: In Vitro Study. *Materials* . 12(9):1448. https://doi: 10.3390/ma12091448.

27) Jayachandran, P. Ilango, S. Suseela, V. Nirmaladevi, R. Shaik, M.R. Khan, M. Khan, M. and Shaik, B.(2023) Green Synthesized Silver Nanoparticle-Loaded Liposome-Based Nanoarchitectonics for Cancer Management: In Vitro Drug Release Analysis. *Biomedicines*. 11(1):217. https://doi: 10.3390/biomedicines11010217.

28) Abullais, Saquib S. Abdullah AlQahtani, N. Ahmad, I. Arora, S. Mohammed, Asif. S. Ahmed Javali, M. and Nisar, N. (2021) Synergistic antibacterial activity of herbal extracts with antibiotics on bacteria responsible for periodontitis. *J Infect Dev Ctries*. 15(11):1685-1693. https://doi: 10.3855/jidc.14904.

29) Baumgartner, A. Planinsek, O. (2021). Application of commercially available mesoporous silica for drug dissolution enhancement in oral drug delivery,*European Journal of Pharmaceutical Sciences*,167,106015,https://doi.org/10.1016/j.ejps.2021.106015.