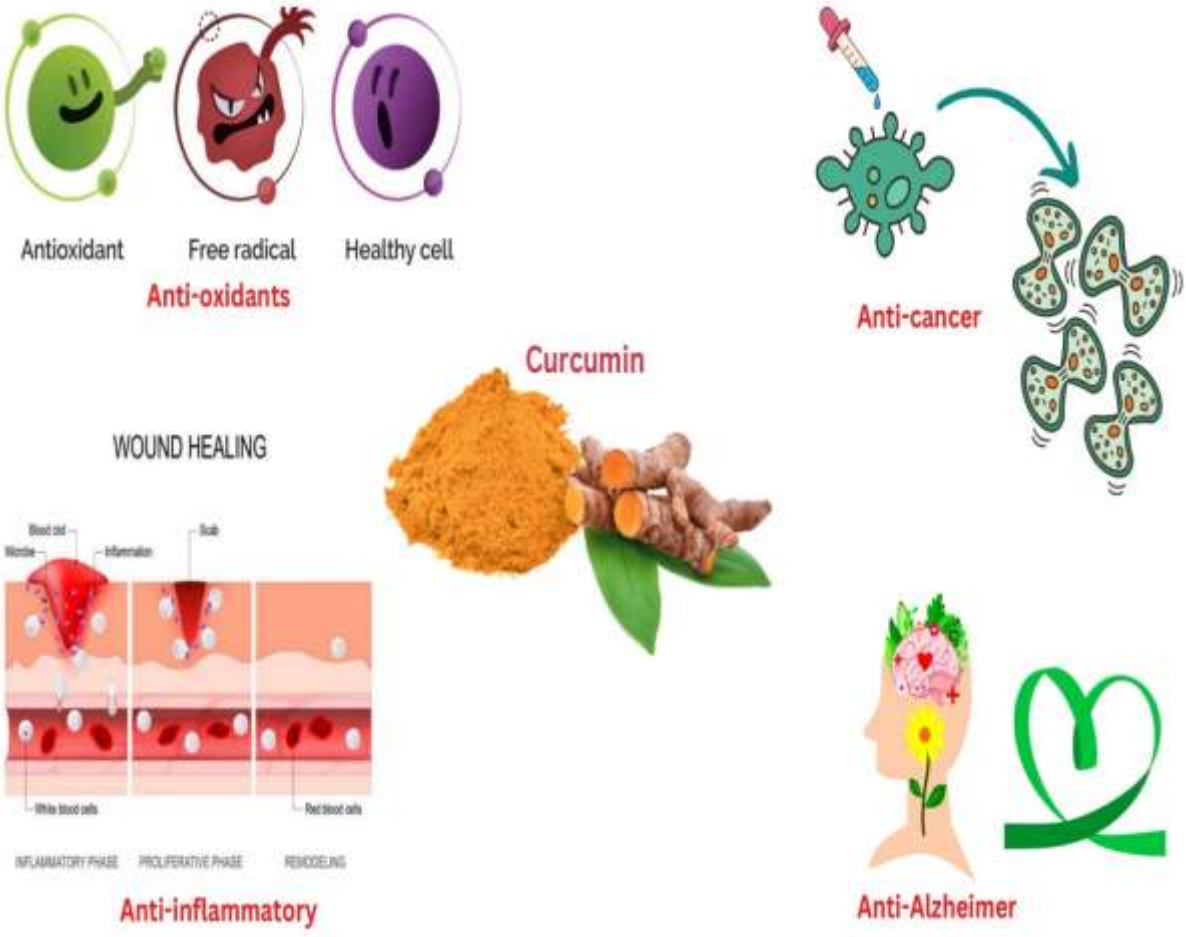
Chapter 6

Amplification of Curcumin Entrapment/Release in Aqueous Counter Charged Gemini Mixtures



6.1. Introduction

As can be seen from the previous studies (Chapters 3 and 4), mixed amphiphilic systems (aggregates) can be preferred over individual components due to their improved benefits such as rich phase behaviour, augmented hydrophobicity, higher packing parameter, elevated aqueous solubility of hydrophobic material, different heating response among others [1–7]. In this connection, various combinations of ionic and non-ionic surfactants are tried which show different degree of variability from ideal mixing [8–10]. However, mixing of contrasting charged surface active moieties results various morphologies and improved uptake of hydrophobic material [1,11–14]. This resulted a renewed interest in '*catanionics'* systems with the point of view of practicability and sustainability [15,16].

Bioavailability of hydrophobic compounds in water is essential in healthcare, chemical industry, pharmacy among others. Various surfactant morphologies are effective solubilizers; however, the solubilization capabilities of vesicles are reported better [17,18]. Bioavailability is a serious problem both with natural and synthetic drugs. Further targeting/driving in a drug or precursor towards affective site is an equally challenging problem.

Curcumin is a natural material that was obtained from turmeric (Curcuma longa), which is a key element in many diets and is believed to possess a variety of therapeutic capabilities [19]. Curcumin has been proven to have antitumor [20], anti-inflammatory [21], and oxidative effects [22], and it has also been demonstrated to be effective in treating mental deterioration [23,24].

A steep rise in research activities over the past two decades involving curcumin has been due to the report that curcumin shows effective antioxidant, anti-inflammatory and anti-

cancer activities [25–29]. It was further shown that curcumin prevents protein aggregation in debilitating ailments e.g., Alzheimer's or Parkinson's [30].

Inadequate solubility/bioavailability of curcumin in water (20 μg/ml) is the key obstacle that hinders its ability to be used for the therapeutic action [31]. Another significant obstacle is the instability in alkaline environments. Such materials deteriorate curcumin quite fast by alkaline hydrolysis followed by the breakdown of the active molecule [32]. Encapsulating curcumin into surfactant aggregates is just an impactful way to tackle water insolubility and stability problems related to curcumin [33–35].

In the present Chapter, curcumin solubility studies are performed in different combinations of gemini surfactants having different spacers/chain lengths. An optimization with respect to composition and spacer is made to perform curcumin *in-vitro* release studies. Kinetic data have been fitted in various models to have a possible mechanism of release. Further anti-oxidation studies of curcumin with or without blended gemini mixture are also investigated in order to shade light on the oxidation phenomenon and its control. The cell proliferation data are obtained by performing MTT assay.

6.2. Results and Discussion

6.2.1. Curcumin Solubilization

UV-visible absorption spectra of curcumin (CUR) in blended geminis, at various compositions, are compiled in Figure 1. For the purpose, various combinations of geminis (12-s-12/10-s-10 + 12-4-12A, s = polymethylene, Eg, Isb or Eda) are used by taking various compositions (x = 0-1).

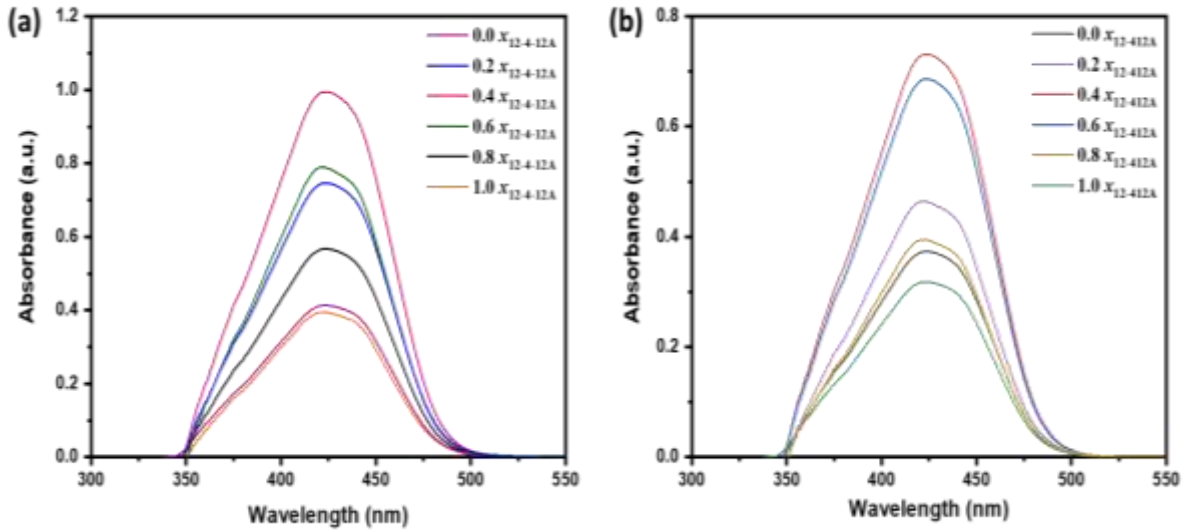


Figure 1. Representative UV-visible spectra drugs solubilized in 10 mM aqueous mixed gemini surfactant system at different mole fractions of anionic gemini ($x_{12\text{-}4\text{-}12A}$): (a) 12-4-12 and (b) 10-4-10.

Figure 1 shows that absorbance is dependent on composition of gemini mixture. However, | absorbance | at the λ_{max} (420 nm) are higher when the two gemini components are nearly equal (x = 0.4 or 0.6). Coincidentally, above compositions produce vesicular aggregates as mentioned in Chapter 4. Hence, vesicles can preferentially be used to achieve increased CUR aqueous solubility (or other drugs in general). Earlier, gemini mixtures have shown

enhanced aqueous solubilities for other water insoluble material such as polycyclic aromatic hydrocarbons (PAHs) and RLX [36–38].

Absorbance data (Figure 1 and similar spectra (not shown) with other gemini combinations) are used to obtain MSR value by the same method as provided in Chapter 5 for RLX. MSR data are used to obtain K_m and ΔG_s^0, and are compiled in Tables 1-4. MSR data show maximum values with cationic geminis (n =10 and 12) are mixed in a specific composition (x = 0.4 or 0.6) with 12-4-12A. Higher MSR values were found with cationic geminis having polymethylene spacer. Further, among polymethylene spacer based cationic geminis, higher MSR observed with 12-4-12 when blended with 12-4-12A. Earlier structural TEM studies show that multilamellar vesicles are formed with this blended combination. This observation hints towards chain length compatibility of the blended mixture and its consequences on aggregate nature with a concomitant effect on MSR data.

Blended mixtures with maximum MSR are chosen for further studies related to curcumin release, anti-oxidant and cell proliferation activity. Kinetic release data are acquired to study release profiles and to justify a kinetic release model.

Table 1. Solubilization parameters (molar solubilization ratio, MSR; micelle-Aqueous Phase Partition Coefficient, $\ln K_m$; Gibbs Free Energy, ΔG_S^0) of **CUR** in aqueous single and mixed gemini surfactants with varying mole fraction of 12-4-12A ($x_{12\text{-}4\text{-}12A}$) at 303 K.

$x_{12-4-12A}$	**Morphology**	**MSR**	**ln K_m**	$-\Delta G_S^0$ **(kJ mol^{-1})**
		12-4-12		
0.0	Ellipsoidal	0.097	6.357	-16.015
0.2	Ellipsoidal	0.164	7.094	-17.869
0.4	Multilamellar vesicle	**0.214**	7.051	-17.763
0.6	Vesicle	0.169	6.856	-17.270
0.8	Ellipsoidal	0.122	6.564	-16.535
1.0	Ellipsoidal	0.085	6.236	-15.710
		12-Eg-12		
0.0	Ellipsoidal	0.103	6.413	-16.156
0.2	Ellipsoidal	0.149	6.743	-16.988
0.4	Vesicle	**0.186**	6.934	-17.469
0.6	Vesicle	0.146	6.727	-16.946
0.8	Ellipsoidal	0.115	6.516	-16.414
1.0	Ellipsoidal	0.085	6.236	-15.710

Table 2. Solubilization parameters (Molar Solubilization Ratio, MSR; micelle-aqueous phase partition coefficient, $\ln K_m$; Gibbs Free Energy, ΔG_s^0) of **CUR** in aqueous single and mixed gemini surfactants with varying mole fraction of 12-4-12A ($x_{12\text{-}4\text{-}12A}$) at 303 K.

$x_{12-4-12A}$	Morphology	MSR	ln K_m	$-\Delta G_s^0$ (kJ mol^{-1})
		12-Isb-12		
0.0	Ellipsoidal	0.105	6.435	-16.211
0.2	Ellipsoidal	0.147	6.733	-16.961
0.4	Vesicle	**0.191**	6.953	-17.516
0.6	Vesicle	0.153	6.765	-17.043
0.8	Ellipsoidal	0.121	6.556	-16.517
1.0	Ellipsoidal	0.085	6.236	-15.710
		12-Eda-12		
0.0	Ellipsoidal	0.092	6.316	-15.909
0.2	Ellipsoidal	0.157	6.786	-17.095
0.4	Rod-shaped	0.166	6.834	-17.214
0.6	Vesicle	**0.198**	6.966	-17.547
0.8	Ellipsoidal	0.119	6.545	-16.485
1.0	Ellipsoidal	0.085	6.236	-15.710

Table 3. Solubilization parameters (molar solubilization ratio, MSR; micelle-Aqueous Phase Partition Coefficient, $\ln K_m$; Gibbs Free Energy, ΔG_s^0) of **CUR** in aqueous single and mixed gemini surfactants with varying mole fraction of 12-4-12A ($x_{12\text{-}4\text{-}12A}$) at 303 K.

$x_{12-4-12A}$	MSR	ln Km	$-\Delta G_s^0$ (kJ mol^{-1})
	10-4-10		
0.0	0.082	6.208	-15.639
0.2	0.088	6.272	-15.799
0.4	**0.164**	6.824	-17.191
0.6	0.148	6.737	-16.973
0.8	0.092	6.313	-15.903
1.0	0.085	6.236	-15.710
	10-Eg-10		
0.0	0.052	5.783	-14.568
0.2	0.061	5.936	-14.954
0.4	**0.137**	6.667	-16.796
0.6	0.098	6.373	-16.054
0.8	0.088	6.278	-15.815
1.0	0.085	6.236	-15.710

Table 4. Solubilization parameters (molar solubilization ratio, MSR; micelle-Aqueous Phase Partition Coefficient, $\ln K_m$; Gibbs Free Energy, ΔG_s^0) of **CUR** in aqueous single and mixed gemini surfactants with varying mole fraction of 12-4-12A ($x_{12\text{-}4\text{-}12A}$) at 303 K.

$x_{12-4-12A}$	MSR	ln Km	$-\Delta G_s^0$ (kJ mol^{-1})
	10-Isb-10		
0.0	0.041	5.555	-13.994
0.2	0.059	5.893	-14.846
0.4	**0.113**	6.501	-16.377
0.6	0.109	6.472	-16.304
0.8	0.092	6.312	-15.906
1.0	0.085	6.236	-15.710
	10-Isb-10		
0.0	0.052	5.781	-14.562
0.2	0.086	6.256	-15.757
0.4	**0.156**	6.780	-17.078
0.6	0.109	6.461	-16.275
0.8	0.095	6.344	-15.980
1.0	0.085	6.236	-15.710

6.2.2. *In-vitro* CUR Release Study

Investigations related to CUR release were conducted using above mentioned vesicular systems with maximum MSR. The profile of CUR release under physiological conditions has been depicted in Figures 2 and 3. The release was observed 144 hours at different time intervals using a trial-and-error experiment. The experiment shows that each mixture displayed a controlled release profile.

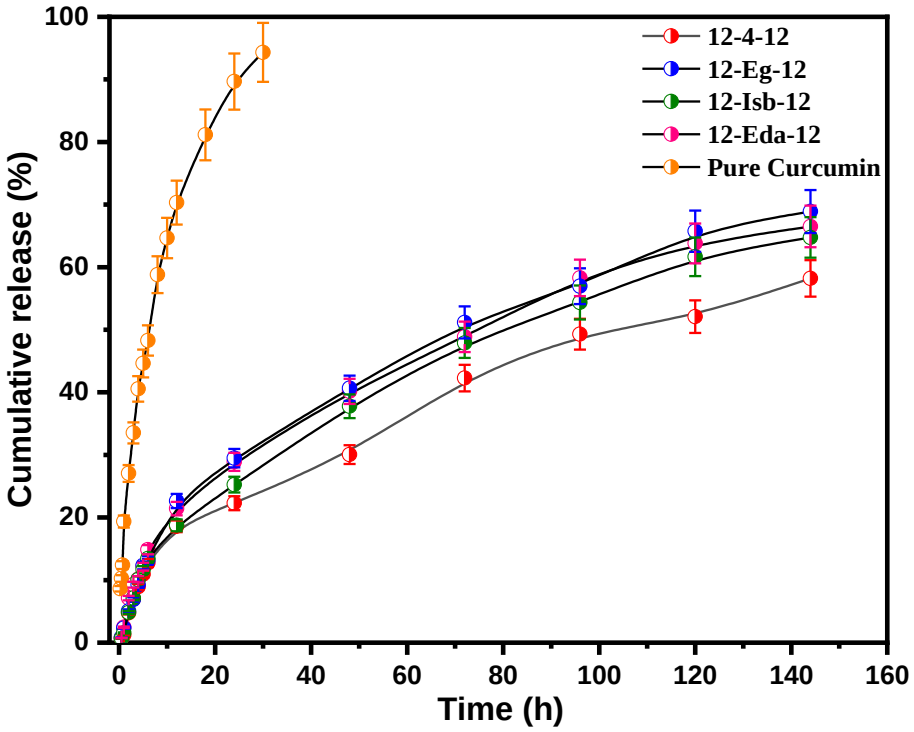


Figure 2. Cumulative release profile of curcumin from micellar formulations (**12-s-12**+12-4-12A) at physiological conditions.

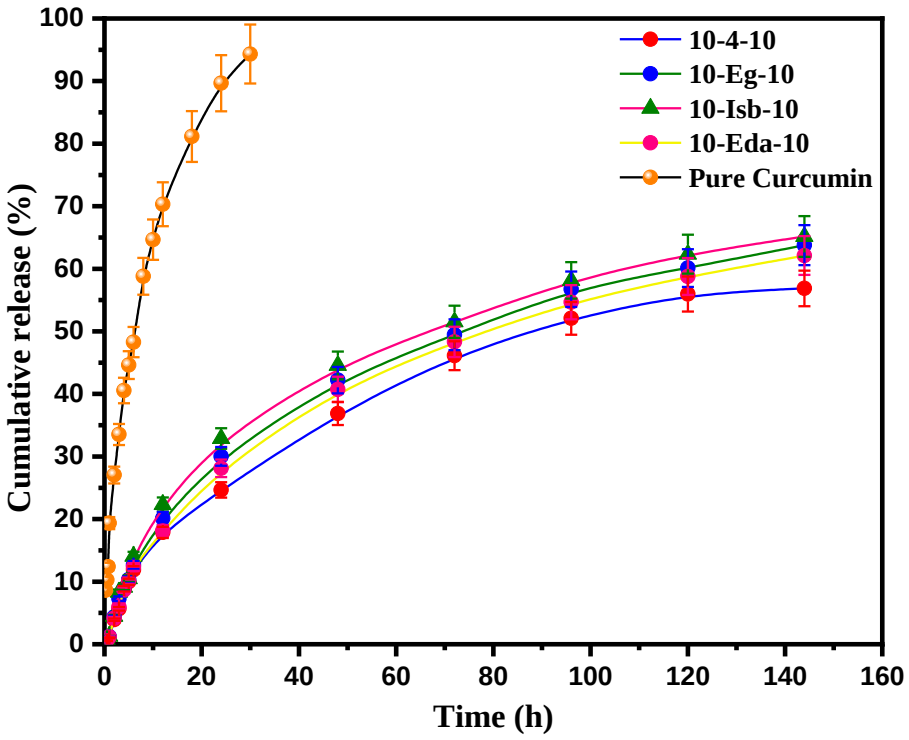


Figure 3. Cumulative release profile of curcumin from micellar formulations (**10-s-10**+12-4-12A) at physiological conditions.

The release data are fitted in various kinetic models as reported in the literature [39]. The fitted profiles are shown in Figures 4 and 5.

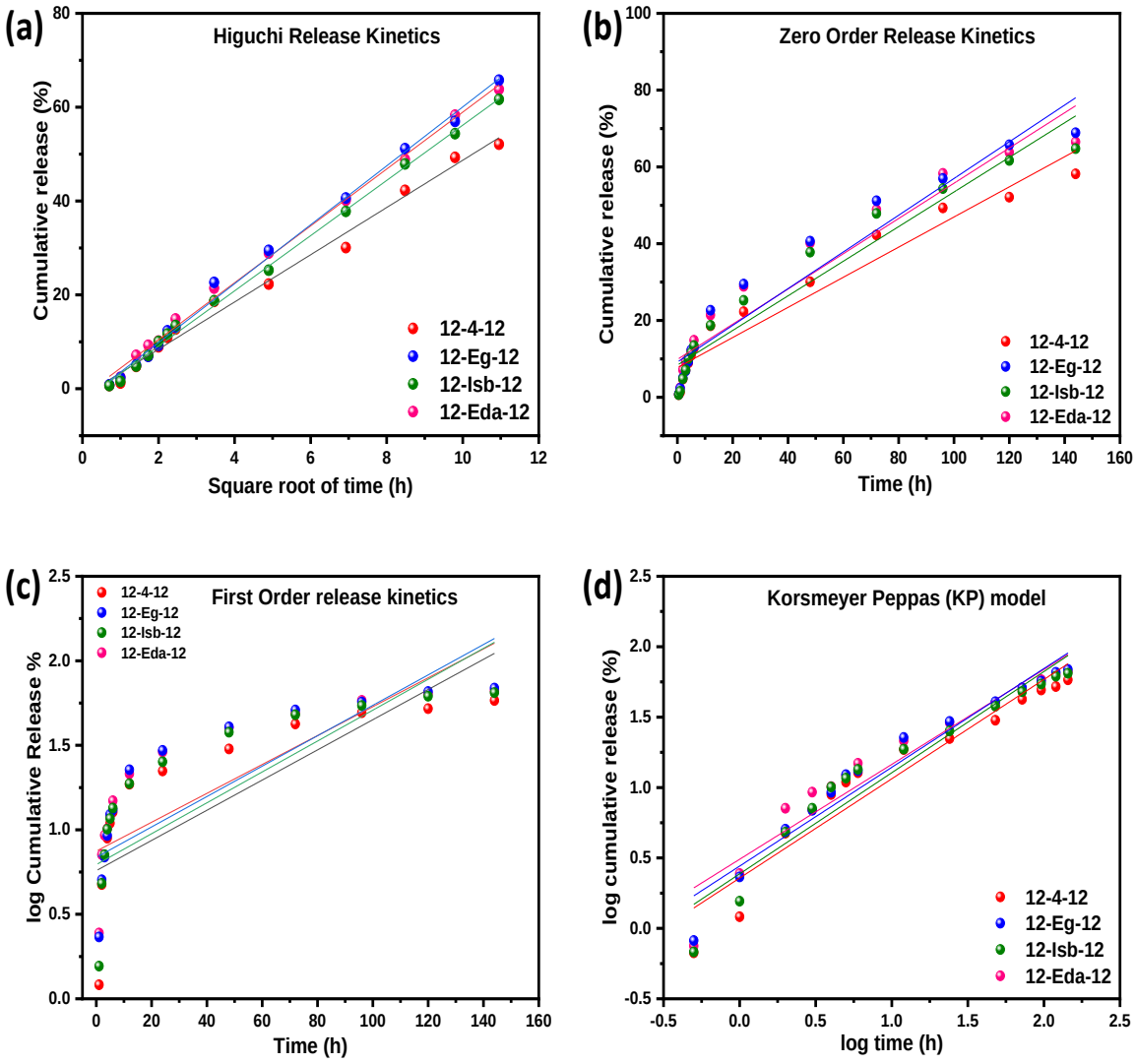


Figure 4. Various kinetics models fitted for **12-s-12** + 12-4-12A mixed micellar formulations.

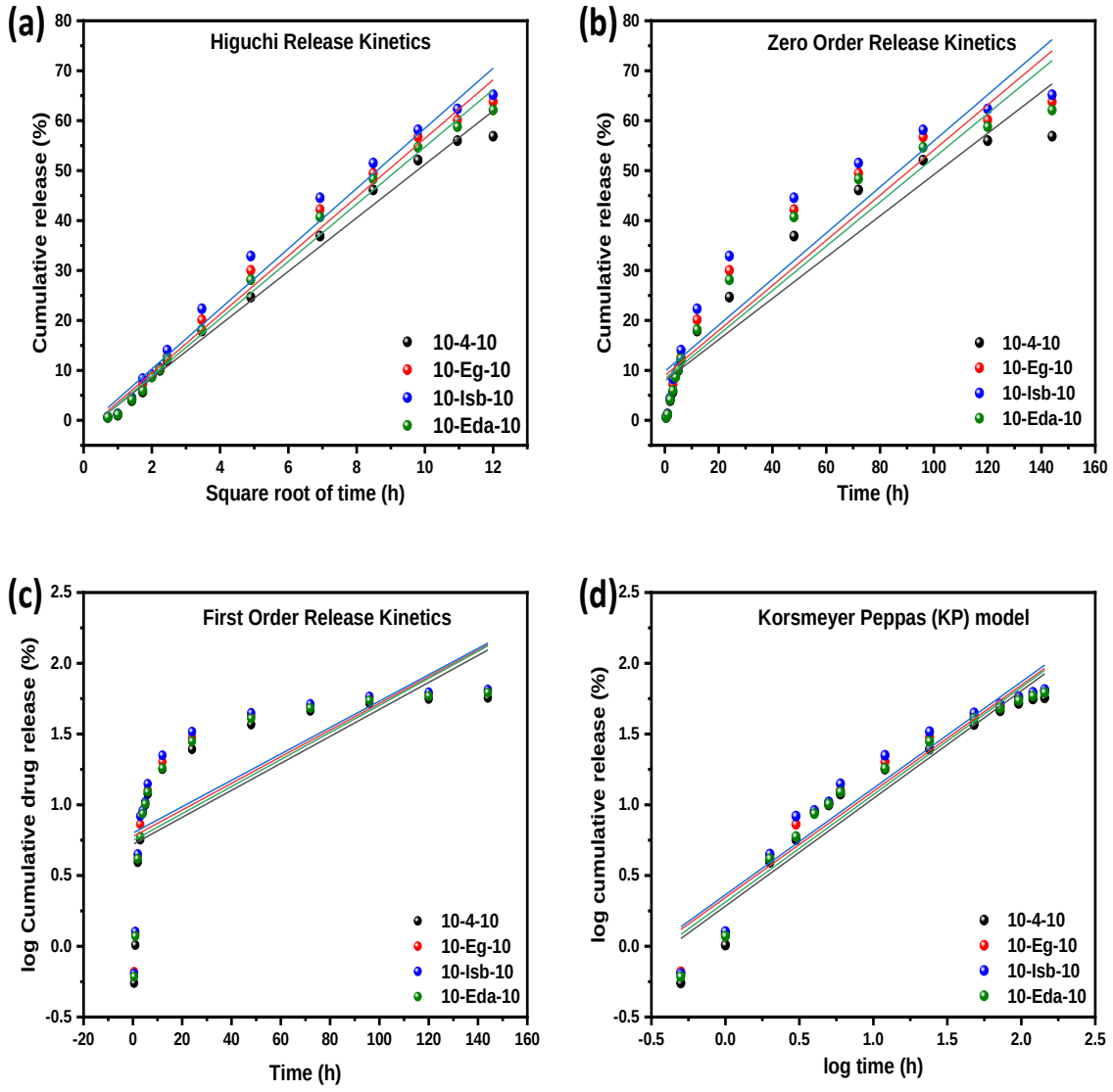


Figure 4. Various kinetics models fitted for **12-s-12** + 12-4-12A mixed micellar formulations.

The computed release parameters using release profiles are summarised in Tables 5 and 6. A perusal of fitted data shows that release profiles better in Higuchi model (good R^2 values near to 1). Higuchi model has been used to show that a sustainable control release is taking place in the blended gemini combinations of specific compositions. Among various spacers of cationic gemini (one component of the blended mixture), polymethylene spacer shows better controlled release of CUR which may be due to stronger hydrophobic environment which resists CUR release (Figures 2 and 3).

Table 5. Different kinetic models depicting the curcumin **(CUR)** release pattern from mixed gemini micelles **(12-s-12 + 12-4-12A)**.

Release Kinetics	**Higuchi**	**Zero-Order**	**First-Order**	**K-peppas**
	12-4-12			
R square	**0.992**	0.915	0.633	0.979
Slope	6.876	1.585	0.110	1.287
Intercept	-4.801	1.452	0.261	0.188
	12-Eg-12			
R square	**0.987**	0.922	0.690	0.928
Slope	7.984	1.889	0.104	1.136
Intercept	-5.915	1.147	0.355	0.309
	12-Isb-12			
R square	**0.986**	0.936	0.622	0.928
Slope	7.003	1.600	0.107	1.277
Intercept	-4.620	1.813	0.305	0.226
	12-Eda-12			
R square	**0.991**	0.916	0.588	0.954
Slope	7.568	1.739	0.099	1.204
Intercept	-4.421	2.489	0.419	0.339

Table 6. Different kinetic models depicting the curcumin **(CUR)** release pattern from mixed gemini micelles **(10-s-10 + 12-4-12A)**.

Release Kinetics	Higuchi	Zero-Order	First-Order	K-peppas
	10-4-10			
R square	**0.988**	0.939	0.648	0.984
Slope	6.667	1.547	0.117	1.342
Intercept	-5.033	0.988	0.182	0.109
	10-Eg-10			
R square	**0.992**	0.922	0.658	0.981
Slope	7.304	1.709	0.114	1.281
Intercept	-5.513	1.024	0.245	0.182
	10-Isb-10			
R square	**0.984**	0.905	0.659	0.976
Slope	8.084	1.903	0.117	1.307
Intercept	-6.322	0.869	0.254	0.189
	10-Eda-10			
R square	**0.990**	0.933	0.654	0.987
Slope	6.735	1.564	0.113	1.284
Intercept	-4.985	1.097	0.219	0.151

6.2.3. *In-vitro* antioxidant activity

DPPH is a widely accepted radical to study antioxidant activity of a drug. The DPPH radical intensity decreases with substance (like an antioxidant) capable of giving protons [40]. CUR with or without blended geminis were taken to observe DPPH scavenge performance by spectrophotometric method at 535 nm. Following equation (1) has been used to study DPPH scavenging abilities at various concentrations of CUR/blended mixtures.

$$DPPH\ Scavenging = \left(1 - \frac{A_i}{A_0}\right) \times 100\% \quad (1)$$

where A_i and A_0 represent the absorbance of DPPH with and without CUR (pure and in blended geminis of different total concentrations (with fixed compositions)). The optimum scavenges efficiency of isolated CUR reaches 89%. However, scavenging capacity of CUR (solubilized in blended geminis) suppressed nearly 95% at the same concentration (10 µg/mL). The relevant data related to above findings are depicted in Figure 6.

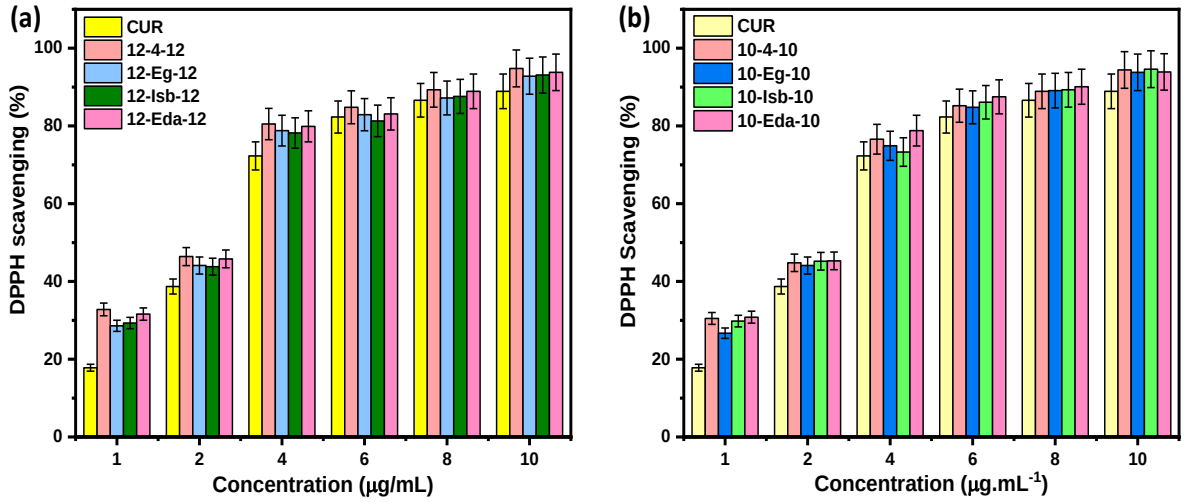
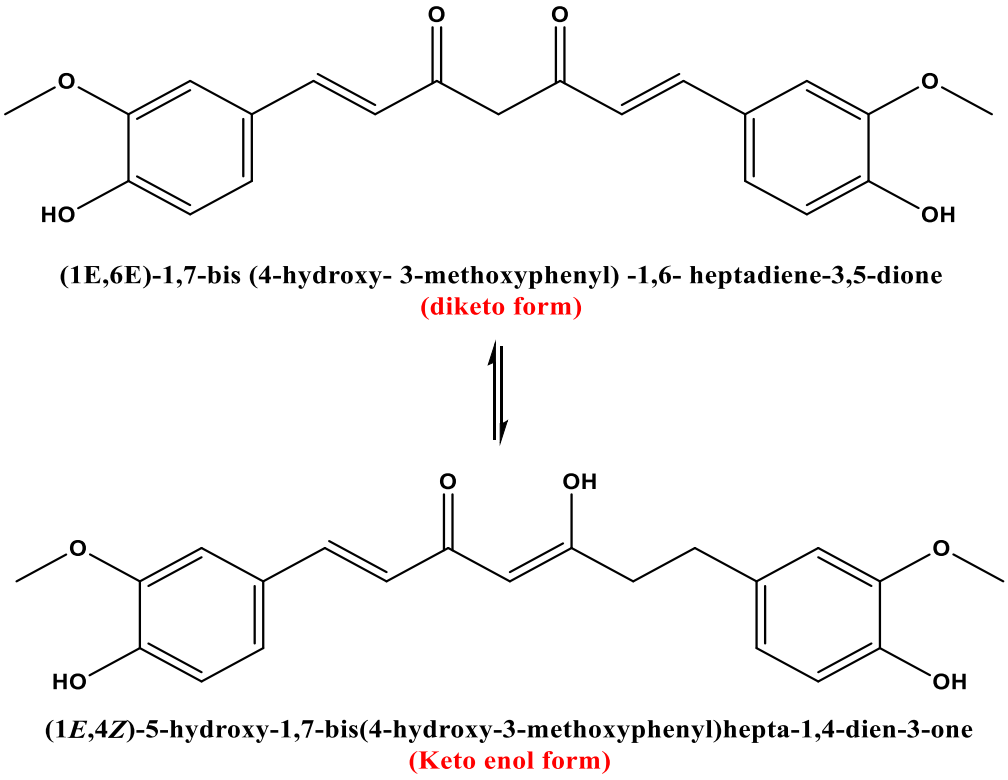


Figure 6. Percentage inhibition of DPPH at various concentrations of pure CUR and CUR solubilized in mixed geminis (a) **12-s-12** + 12-4-12A and (b) **10-s-10** + 12-4-12A.

This capability of curcumin to neutralise free radicals seems to be due to dehydrogenation of curcumin, which occurs at the keto-enol position (Scheme 1) [41]. The potential improvement of the antioxidant potential of CUR by the blended gemini formulation may be due to solubilization environment which resist scavenging activity. Probably, increased CUR solubility and its concomitant effect of aggregate size seems responsible for the

scavenging activity modulation. The vesicle bilayer provides a more favourable environment for the interaction of curcumin and DPPH. Therefore, the capability of a keto-enol unit of CUR to diminish DPPH was associated with its highest proton-donating capabilities.



Scheme 1. Keto-enol tautomeric forms of Curcumin.

6.2.4. *In-vitro* Cell Proliferation Activity

A tetrazolium salt MTT test was employed to assess the cytotoxic effects of the optimised drug, mixed geminis (without CUR), and CUR-solubilized blended geminis on MCF-7 breast cancer cells. Reduction of cell proliferation as a percentage was assessed after 24 hours of treatment on MCF-7 cells, as demonstrated in Figures 7 and 8. CUR solubilized blended mixtures of geminis show better cell proliferation than pure CUR or pure blended mixtures. The data are fitted (not shown) to acquire IC_{50} values.

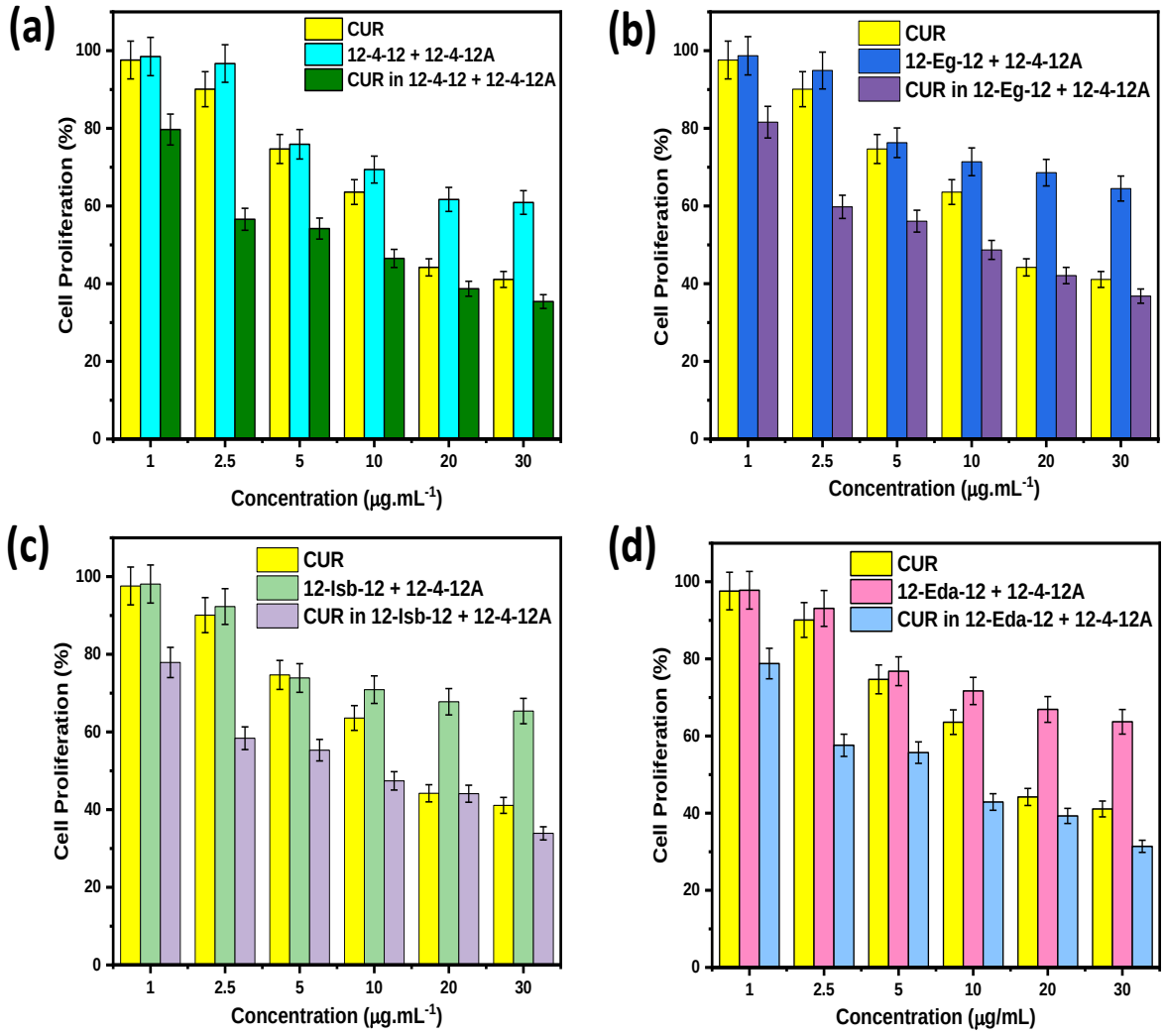


Figure 7. Cell proliferation activity of pure curcumin, mixed geminis and curcumin solubilized in mixed geminis (a)12-4-12 (b) 12-Eg-12, (c) 12-Isb-12 and (d) 12-Eda-12 towards MCF-cells.

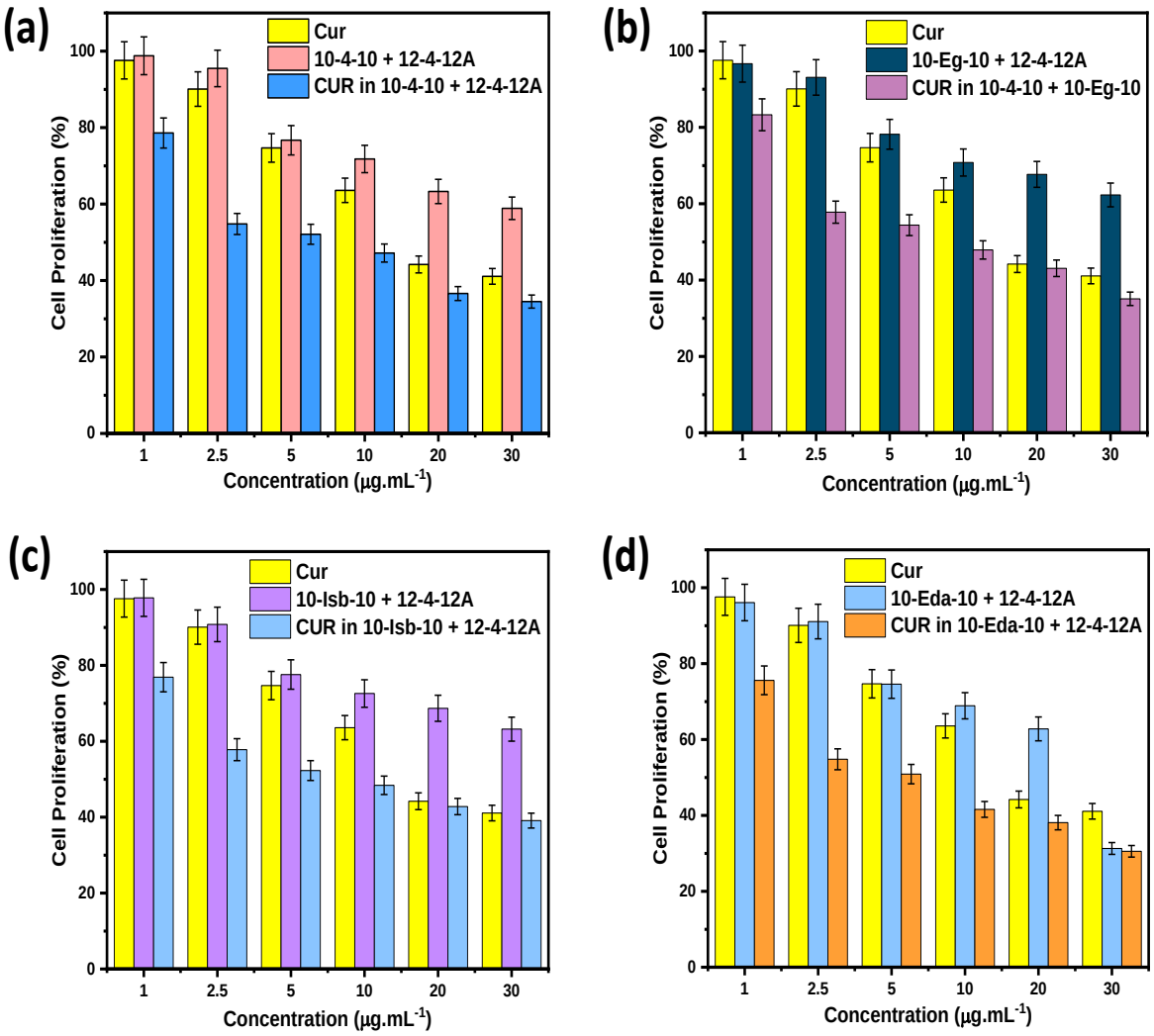


Figure 8. Cell proliferation activity of pure curcumin, mixed geminis and curcumin solubilized in mixed geminis (a)12-4-12 (b) 12-Eg-12, (c) 12-Isb-12 and (d) 12-Eda-12 towards MCF-cells.

IC_{50} values obtained from cell proliferation experiment are compiled in Table 7. Perusal of data shows that CUR solubilized blended geminis performs better than pure CUR/blends. Blend containing equal alkyl chains (n=12), in counter charged geminis, shows best performance among the mixtures used by taking various components. The nature of the spacer

(Isb in the present case) has also contribution to dictate lower IC_{50} value. This may be plausibly due to the hydrophilic nature of the spacer among the class studied here. Comparison of IC_{50} data (Table 7) with other micellar systems [42–44] shows that blended micelles of equal chain geminis performs better than the reported systems of polymer/surfactant based material.

Table 7. The half maximal inhibitory concentration (IC_{50}) of curcumin (CUR), mixed geminis and CUR solubilized in mixed geminis towards the MCF-7 cells.

System	**IC_{50} (µg/mL)**
Pure Curcumin	21.048
12-4-12 + 12-4-12A	33.441
Curcumin in 12-4-12 + 12-4-12A	8.345
12-Eg-12 + 12-4-12A	38.832
Curcumin in 12-Eg-12 + 12-4-12A	9.621
12-Isb-12 + 12-4-12A	40.633
Curcumin in 12-Isb-12 + 12-4-12A	**8.154**
12-Eda-12 + 12-4-12A	38.552
Curcumin in 12-Eda-12 + 12-4-12A	10.139
10-4-10 + 12-4-12A	32.703
Curcumin in 10-4-10 + 12-4-12A	12.013
10-Eg-10 + 12-4-12A	37.436
Curcumin in 10-Eg-10 + 12-4-12A	14.342
10-Isb-10 + 12-4-12A	39.244
Curcumin in 10-Isb-10 + 12-4-12A	14.318
10-Eda-10 + 12-4-12A	22.085
Curcumin in 10-Eda-10 + 12-4-12A	10.203

References:

[1] E.W. Kaler, A.K. Murthy, B.E. Rodriguez, J.A.N. Zasadzinski, Spontaneous vesicle formation in aqueous mixtures of single-tailed surfactants, Science (80-.). 245 (1989) 1371–1374.

[2] H. Edlund, A. Sadaghiani, A. Khan, Phase behavior and phase structure for catanionic surfactant mixtures: dodecyltrimethylammonium chloride− sodium nonanoate− water system, Langmuir. 13 (1997) 4953–4963.

[3] Y. Yan, T. Lu, J. Huang, Recent advances in the mixed systems of bolaamphiphiles and oppositely charged conventional surfactants, J. Colloid Interface Sci. 337 (2009) 1–10.

[4] J. Bhattacharjee, V.K. Aswal, P.A. Hassan, R. Pamu, J. Narayanan, J. Bellare, Structural evolution in catanionic mixtures of cetylpyridinium chloride and sodium deoxycholate, Soft Matter. 8 (2012) 10130–10140.

[5] S. Kumar, H. Patel, Morphological transitions in aqueous CTAB–NaDC system: Macroscopic and microscopic studies, J. Mol. Liq. 190 (2014) 74–80. https://doi.org/https://doi.org/10.1016/j.molliq.2013.10.020.

[6] S. Singh, S.K. Yadav, K. Parikh, A. Desai, S. Dixit, S. Kumar, Mixed micellization/clouding assisted solubilization of polycyclic aromatic hydrocarbon: Potential in environmental remediation, J. Mol. Liq. 272 (2018) 413–422. https://doi.org/https://doi.org/10.1016/j.molliq.2018.09.022.

[7] J.N. Israelachvili, D.J. Mitchell, B.W. Ninham, Theory of self-assembly of hydrocarbon amphiphiles into micelles and bilayers, J. Chem. Soc. Faraday Trans. 2 Mol. Chem. Phys. 72 (1976) 1525–1568. https://doi.org/10.1039/F29767201525.

[8] K. Maiti, S.C. Bhattacharya, S.P. Moulik, A.K. Panda, Physicochemical studies on ion-pair amphiphiles: Solution and interfacial behaviour of systems derived from sodium dodecylsulfate and n-alkyltrimethylammonium bromide homologues, J. Chem. Sci. 122 (2010) 867–879.

[9] K. Manna, C.-H. Chang, A.K. Panda, Physicochemical studies on the catanionics of alkyltrimethylammonium bromides and bile salts in aqueous media, Colloids Surfaces

A Physicochem. Eng. Asp. 415 (2012) 10–21.

[10] W.H. Ansari, N. Fatma, M. Panda, Kabir-ud-Din, Solubilization of polycyclic aromatic hydrocarbons by novel biodegradable cationic gemini surfactant ethane-1,2-diyl bis(N,N-dimethyl-N-hexadecylammoniumacetoxy) dichloride and its binary mixtures with conventional surfactants, Soft Matter. 9 (2013) 1478–1487. https://doi.org/10.1039/C2SM26926K.

[11] H. Yin, Z. Zhou, J. Huang, R. Zheng, Y. Zhang, Temperature-induced micelle to vesicle transition in the sodium dodecylsulfate/dodecyltriethylammonium bromide system, Angew. Chemie Int. Ed. 42 (2003) 2188–2191.

[12] A. Boudier, P. Castagnos, E. Soussan, G. Beaune, H. Belkhelfa, C. Ménager, V. Cabuil, L. Haddioui, C. Roques, I. Rico-Lattes, Polyvalent catanionic vesicles: exploring the drug delivery mechanisms, Int. J. Pharm. 403 (2011) 230–236.

[13] S.K. Yadav, K. Parikh, S. Kumar, Solubilization potentials of single and mixed oppositely charged gemini surfactants: A case of polycyclic aromatic hydrocarbons, Colloids Surfaces A Physicochem. Eng. Asp. 514 (2017) 47–55. https://doi.org/https://doi.org/10.1016/j.colsurfa.2016.11.042.

[14] T. Yoshimura, A. Ohno, K. Esumi, Mixed micellar properties of cationic trimeric-type quaternary ammonium salts and anionic sodium n-octyl sulfate surfactants, J. Colloid Interface Sci. 272 (2004) 191–196. https://doi.org/https://doi.org/10.1016/j.jcis.2003.12.021.

[15] S. Ghosh, B. Ambade, A. Ray, Stable catanionic vesicles as drug delivery vehicle, Sci. Adv. Mater. 5 (2013) 1837–1846.

[16] M. Jain, A. Marfatia, N. Imam, D. Ray, V.K. Aswal, N.Y. Patel, V.H. Raval, S.K. Kailasa, N.I. Malek, Ionic liquid-based catanionic vesicles: A de novo system to judiciously improve the solubility, stability and antimicrobial activity of curcumin, J. Mol. Liq. 341 (2021) 117396.

[17] P. Tanner, P. Baumann, R. Enea, O. Onaca, C. Palivan, W. Meier, Polymeric vesicles: from drug carriers to nanoreactors and artificial organelles, Acc. Chem. Res. 44 (2011) 1039–1049.

[18] V. Kumar, K. Kumar, A. Joshi, D. Teotia, A comprehensive review on liposomes: A vesicular system for drug delivery, GSC Biol. Pharm. Sci. 18 (2022) 331–337.

[19] R.K. Maheshwari, A.K. Singh, J. Gaddipati, R.C. Srimal, Multiple biological activities of curcumin: a short review, Life Sci. 78 (2006) 2081–2087.

[20] M.A. Tomeh, R. Hadianamrei, X. Zhao, A review of curcumin and its derivatives as anticancer agents, Int. J. Mol. Sci. 20 (2019) 1033.

[21] V.P. Menon, A.R. Sudheer, Antioxidant and anti-inflammatory properties of curcumin, Mol. Targets Ther. Uses Curcumin Heal. Dis. (2007) 105–125.

[22] T. Ak, I. Gülçin, Antioxidant and radical scavenging properties of curcumin, Chem. Biol. Interact. 174 (2008) 27–37.

[23] L. Baum, C.W.K. Lam, S.K.-K. Cheung, T. Kwok, V. Lui, J. Tsoh, L. Lam, V. Leung, E. Hui, C. Ng, Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease, J. Clin. Psychopharmacol. 28 (2008) 110–113.

[24] V.K. Soni, A. Mehta, D. Shukla, S. Kumar, N.K. Vishvakarma, Fight COVID-19 depression with immunity booster: Curcumin for psychoneuroimmunomodulation, Asian J. Psychiatr. 53 (2020) 102378.

[25] A.J. Ruby, G. Kuttan, K.D. Babu, K.N. Rajasekharan, R. Kuttan, Anti-tumour and antioxidant activity of natural curcuminoids, Cancer Lett. 94 (1995) 79–83.

[26] R.C. Lantz, G.J. Chen, A.M. Solyom, S.D. Jolad, B.N. Timmermann, The effect of turmeric extracts on inflammatory mediator production, Phytomedicine. 12 (2005) 445–452.

[27] B.B. Aggarwal, K umar A, Bharti AC. A nticancer P otential of C urcumin: Preclinical and Clinical Studies, Anticancer Res. 23 (2003) 363–398.

[28] M. Shi, Q. Cai, L. Yao, Y. Mao, Y. Ming, G. Ouyang, Antiproliferation and apoptosis induced by curcumin in human ovarian cancer cells, Cell Biol. Int. 30 (2006) 221–226.

[29] Y.-J. Surh, Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review, Food Chem. Toxicol. 40

(2002) 1091–1097.

[30] M. Masuda, N. Suzuki, S. Taniguchi, T. Oikawa, T. Nonaka, T. Iwatsubo, S. Hisanaga, M. Goedert, M. Hasegawa, Small molecule inhibitors of α-synuclein filament assembly, Biochemistry. 45 (2006) 6085–6094.

[31] P. Anand, A.B. Kunnumakkara, R.A. Newman, B.B. Aggarwal, Bioavailability of curcumin: problems and promises, Mol. Pharm. 4 (2007) 807–818.

[32] A. Siviero, E. Gallo, V. Maggini, L. Gori, A. Mugelli, F. Firenzuoli, A. Vannacci, Curcumin, a golden spice with a low bioavailability, J. Herb. Med. 5 (2015) 57–70.

[33] M.H.M. Leung, H. Colangelo, T.W. Kee, Encapsulation of curcumin in cationic micelles suppresses alkaline hydrolysis, Langmuir. 24 (2008) 5672–5675.

[34] F. Cuomo, L. Perugini, E. Marconi, M.C. Messia, F. Lopez, Enhanced curcumin bioavailability through nonionic surfactant/caseinate mixed nanoemulsions, J. Food Sci. 84 (2019) 2584–2591.

[35] A. Kumar, G. Kaur, S.K. Kansal, G.R. Chaudhary, S.K. Mehta, Enhanced solubilization of curcumin in mixed surfactant vesicles, Food Chem. 199 (2016) 660–666.

[36] S. Singh, A. Bhadoria, K. Parikh, S.K. Yadav, S. Kumar, V.K. Aswal, S. Kumar, Self-Assembly in Aqueous Oppositely Charged Gemini Surfactants: A Correlation between Morphology and Solubilization Efficacy, J. Phys. Chem. B. 121 (2017) 8756–8766. https://doi.org/10.1021/acs.jpcb.7b03989.

[37] S. Singh, K. Parikh, S. Kumar, V.K. Aswal, S. Kumar, Spacer nature and composition as key factors for structural tailoring of anionic/cationic mixed gemini micelles: Interaction and solubilization studies, J. Mol. Liq. 279 (2019) 108–119. https://doi.org/https://doi.org/10.1016/j.molliq.2019.01.097.

[38] B. Patel, S. Singh, K. Parikh, V. Chavda, D. Ray, V.K. Aswal, S. Kumar, Micro-Environment mapping of mole fraction inspired contrasting charged aqueous gemini micelles: A drug solubilization/release study, J. Mol. Liq. 363 (2022) 119885. https://doi.org/https://doi.org/10.1016/j.molliq.2022.119885.

[39] P. Singla, S. Garg, S. Kaur, N. Kaur, N. Kaur, V.K. Aswal, E. Velliou, H. Kaur, M. Peeters, R.K. Mahajan, Unusual solubilization capacity of hydrophobic drug olanzapine in polysorbate micelles for improved sustained drug release, J. Mol. Liq. 359 (2022) 119256.

[40] P. Goupy, C. Dufour, M. Loonis, O. Dangles, Quantitative kinetic analysis of hydrogen transfer reactions from dietary polyphenols to the DPPH radical, J. Agric. Food Chem. 51 (2003) 615–622.

[41] S. V Jovanovic, S. Steenken, C.W. Boone, M.G. Simic, H-atom transfer is a preferred antioxidant mechanism of curcumin, J. Am. Chem. Soc. 121 (1999) 9677–9681.

[42] R. Yang, S. Zhang, D. Kong, X. Gao, Y. Zhao, Z. Wang, Biodegradable polymer-curcumin conjugate micelles enhance the loading and delivery of low-potency curcumin, Pharm. Res. 29 (2012) 3512–3525.

[43] A. Sahu, N. Kasoju, U. Bora, Fluorescence study of the curcumin− casein micelle complexation and its application as a drug nanocarrier to cancer cells, Biomacromolecules. 9 (2008) 2905–2912.

[44] A. Sahu, N. Kasoju, P. Goswami, U. Bora, Encapsulation of curcumin in Pluronic block copolymer micelles for drug delivery applications, J. Biomater. Appl. 25 (2011) 619–639.