ARTICLE

pH Responsive Shellac for Pharmaceutical Applications: Preparation, Thermal Stability and Controlled Release of 5-Amino salicylic Acid

A. Barik[1], T. Patnaik[2], P. Parhi[1] and R.K. Dey[3,✉]

Asian Pub. Corp.

www.asianpubs.org

Asian Journal of Organic & Medicinal Chemistry

Volume: 1 Year: 2016
Issue: 2 Month: April-June
pp: 45-50
DOI: http://dx.doi.org/10.14233/ajomc.2016.AJOMC-P8

Received: 17 February 2016
Accepted: 15 June 2016
Published: 2 July 2016

ABSTRACT

The present investigation reports design of a new pH responsive polymeric material from shellac for pharmaceutical applications. The material was prepared from the combination of shellac and glycine. Acrylic acid was used to incorporate pH responsive characteristics in the material. The material was characterized using Fourier transform infrared spectroscopy, thermogravimetric analysis and scanning electron micrograph techniques. The thermal stability and the kinetics of material decomposition were evaluated using various mathematical models. The kinetics of controlled release of 5-amino salicylic acid was studied in buffer medium using Fick's model equation.

KEYWORDS

Shellac, Glycine, pH responsive, Controlled release, 5-Amino salicylic acid.

INTRODUCTION

Plant based materials and various materials derived from biological sources are preferred in biomedical field of research due to number of advantages [1]. In this regard, amino acid, a natural biomolecule, find immense importance in pharmaceutical applications [2]. Amino acids can interact with other molecules by covalent coupling, electro-static binding and physical adsorption process [3]. The self-assemble properties of amino acid molecules are often helpful in controlling the surface charge of biomaterials [2]. It is further interesting in view of the fact that introduction of amino acids bridges in the matrix stabilizes the final structure of the molecule.

On the other hand, polymers *e.g.*, cellulose, alginate, *etc.*, which are of natural origin, find wide applications as biomaterials/carrier matrices (controlled release applications) in various pharmaceutical field of research [1,4,5]. Appropriate design and fabrication of materials are often helpful in releasing physically entrapped drug molecules with well-defined kinetics [6]. It may be noted that a number of studies [7,8] have also reported the use of proteins, amino acids *etc.*, in combination with polymeric materials that can be helpful in improving the

Author affiliations:

[1]Department of Chemistry, Ravenshaw University, Cuttack-753 003, India
[2]Department of Chemistry, Stewart Science College, Cuttack-753 008, India
[3]Centre for Applied Chemistry, Central University of Jharkhand, Ranchi-835 205, India

✉To whom correspondence to be addressed:

Fax: +91 671 2306624
E-mail: rkdey@rediffmail.com

Available online at: http://ajomc.asianpubs.org

material efficiency, selectivity for particular application purpose. Simi and Abraham [8] studied the cross-linked protein crystals immobilized in a non-toxic hydrophilic and natural biopolymer matrix to prepare pH sensitive beads for pharmaceutical applications. Such kind of matrices also provide space for bifunctionalized reagent to form strong covalent bond between the free amino acid groups in the protein molecule to preserve the crystalline structure. The material was used for oral sustain delivery of encapsulated enzyme crystals. Pérez *et al*. [9] reported a new strategy for the covalent immobilization of active peptide moiety to polymeric chain through intermediacy. The new co-polymeric network structure promoted the regenerative processes in the nervous system. In recent development, covalently modified hydrogel blend of hyaluronan-methyl cellulose with peptide material has also shown interesting application in promoting growth factors required for bioactive factor immobilization [10].

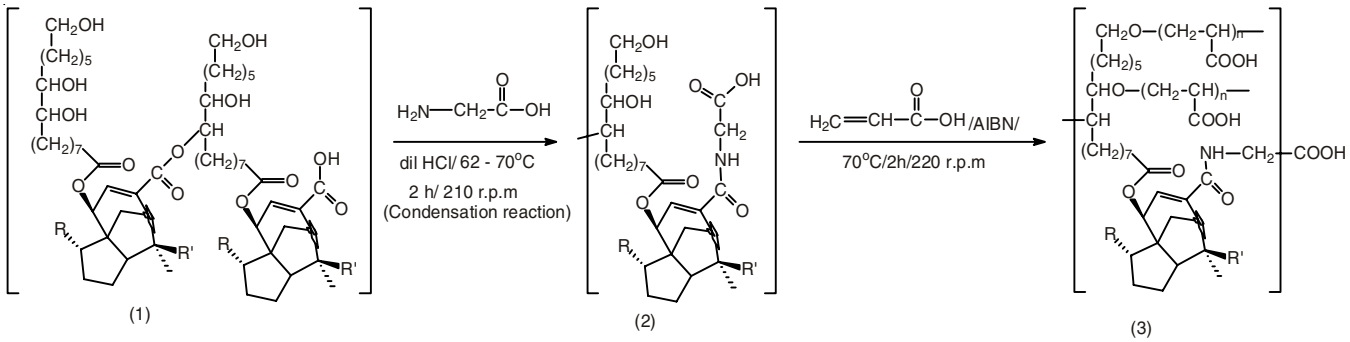
There is a considerable scope for making new carrier matrix for control drug delivery by combining the property of selective polymeric material and biomolecules. In this aspect, glycine (Gly) is an important amino acid, which possesses amphoteric characteristics. The presence of such kind of functional groups (-COOH and -NH_2) in the molecule can be helpful in controlling the surface morphology of final product molecules [3]. Preparation of porous scaffold materials, by photo-polymerization process using glycine, have previously been reported [11]. The polymeric materials were found to be non-cytotoxic as well as biodegradable. Further, reports are also available regarding preparation of new kind of amino acid based cross-linked polymeric gel that have been used as stimuli responsive material [12]. In particular case, polymeric gels containing amino acids reported to show remarkable property of switching over from organo-gel to hydrogel by simple deprotonating mechanism [12]. The degree of swelling of the polymeric material in physiological medium is dependent upon the pendant amino acid moiety.

The present investigation reports the preparation of a new chemically modified shellac as a carrier matrix for controlled release of drug molecules. Shellac (Sh) was chemically modified using glycine and pH responsive characteristics in the material have been incorporated using acrylic acid (AA). The use of natural shellac in developing new biomaterial is currently a field of immense interest due to a number of bio related properties of shellac such as non-toxicity, biodegradability and food values associated with it [13]. Shellac is a natural biocompatible polymer derived from secretion of lac insects *Laccifer laca* (Kerr). The chemical structure of shellac contains a number of carboxylic acid and hydroxyl groups [14]. Shellac is hydrophilic in characteristics and used in formulation of various colon specific drug carrier matrices [15,16]. However, proper development and wide commerical exploitation of shellac based materials, particularly in biomedical/pharmaceutical field of research, is relatively new [17]. Thus, the material prepared herein, reports the synthesis using simple reaction schemes carried out in fewer steps. The prepared material was characterized using FTIR, TGA and SEM. Further, thermal stability and kinetics of decomposition of material was also evaluated using various mathematical models such as Coats-Redfern (CR) and Kissinger-Akahira-Sonuse (KAS). The study can be helpful in designing the material for various high end applications. The work also reports the control release of 5-amino salicylic acid (5-ASA), a model colon specific drug, from the Sh-Gly-AA matrix and the release process was evaluated using mathematical model.

EXPERIMENTAL

Glycine was procured from Sigma Aldrich. Acrylic acid was obtained from Acros Organics and used after distillation under reduced pressure. Shellac was a gift sample from Indian Institute of Natural Research in Gum (IINRG), Ranchi. All other chemical were of AR grade and used as such without purification. The polymeric material was prepared in two steps as shown in reaction **Scheme-I**. The first step constitute condensation reaction of shellac (1) with glycine to produce a gray coloured condensation product (2) (Sh-Gly) with 62 % yield. In step 2, product 2 was reacted with acrylic acid (1:2 molar proportion) to produce addition product (3), Sh-Gly-AA, with about 41 % yield. All the products were collected washed with cold ethanol and vacuum dried for 24 h.

FT-IR of the sample material was recorded using IR-Prestige 21 (Shimadzu) at room temperature. The Differential Scanning Calorimetric study was conducted on a TA Instrument, Model Q 10, USA, in nitrogen environment. An UV-visible spectrophotometer (Perkin Elmer, Lambda-25) was used for measurement of aliquot of drug sample. The scanning Electron Microscopic (SEM) study of the sample materials were obtained on a JSM 63690LV, under vacuum, accelerated at 20 kV. pH measurement was done using Systronic digital pH meter, model 335 equipped with calomel glass electrode.



Scheme-I: Reaction pathway for the synthesis of Sh-Gly-AA

Thermogravimetric analysis (TGA) of sample material was performed on a Shimadzu instrument (DTG 60) in nitrogen atmosphere under flow of 20 mL min^{-1} and heating rate of 10 °C min^{-1}. Dissolution test was carried out using the fully automated dissolution system (Electrolab, Model No. TOT-08L).

Controlled release of 5-amino salicylic acid: The *in vitro* kinetics was studied using fully automated dissolution apparatus (Electrolab, Model No. TOT-08L) equipped with eight baskets. Dissolution rates were measured at 37 °C under 100 rpm speed. Dissolution was carried out using the fully automated dissolution system. *in vitro* cumulative release studies of 5-amino salicylic acid was measured by placing a fixed weight of material loaded with 5-amino salicylic acid in various buffer solutions simulating gastric fluid and simulating intestinal fluid at 37 °C. At definite time intervals, aliquot absorbance was checked using UV spectrophotometer at fixed λ_{max} value of 214 nm. All data points were means of three determinations and only less than 3 % variation from the mean was observed in all cases.

RESULTS AND DISCUSSION

The structure (Fig. 1) shows polyester unit consisting of aleuritic acid part and terpenic acid part. Correspondingly, analysis of C, H and N content shows the % of C and H as 28.3, 16.5. No nitrogen was detected as an element in the sample of shellac. The material Sh-Gly-AA shows the values as (%) C: 34.2, H: 28.8, N: 12.1.

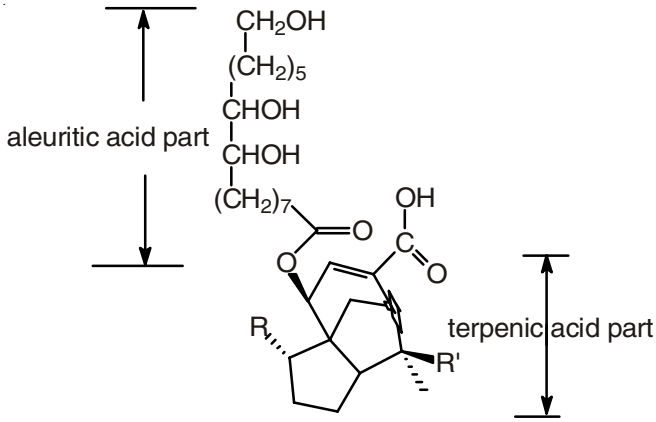


Fig. 1. Structure of shellac showing aleuritic acid part and terpenic acid part [Ref. 25]

FTIR spectroscopy: The FTIR spectra is useful for elucidating the basic structural characteristic of materials. The FTIR spectrum of shellac (Sh), Sh-Gly and Sh-Gly-AA is shown in the Fig. 2. The FTIR shows various bands related to shellac. Presence of broad peaks at 3450 cm^{-1} attributed the presence of hydroxyl groups, $\nu(O\text{-}H)_{str}$, in shellac moiety. The peaks, observed at 1720 cm^{-1} $\nu(C{=}O)_{str}$ and 1250 cm^{-1} $\delta(C\text{-}O)_{def}$, indicated the presence of carboxylic functional group in shellac. Peaks observed at 2843 and 2905 cm^{-1} were assigned to $\nu(C\text{-}H)_{str}$ of methylene ($–CH_2$) and methyl ($–CH_3$) groups, respectively. Other characteristics peaks attributed to bending/deformation mode $\delta(CH_2$ and $CH_3)$ of methylene and methyl groups were observed in the range 1500-1400 cm^{-1}. Vibrational band observed at 1100 cm^{-1} was attributed to ester linkage of

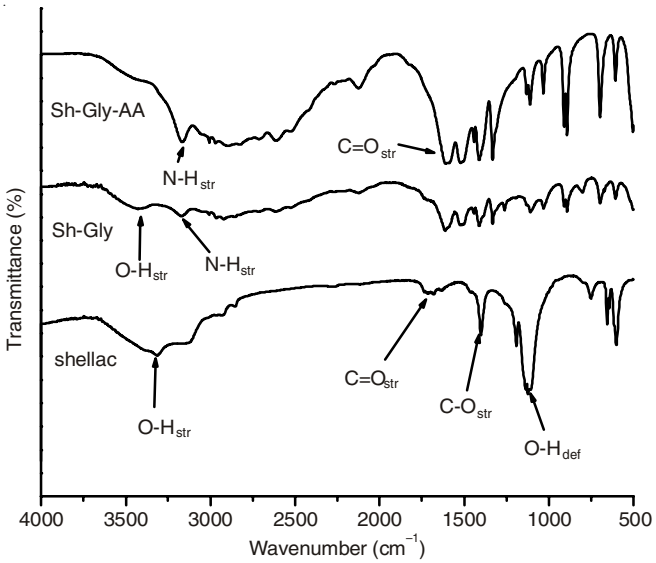


Fig. 2. FTIR spectrum of (a): Shellac (Sh); (b) Sh-Gly and (c):Sh-Gly-AA

shellac moiety. FTIR spectra of Sh-Gly shows peaks attributed to presence of both shellac and glycine in the material. Peak observed in the range 3350-3310 and 1250-1020 cm^{-1} attributed to $\nu(N\text{-}H)_{str}$ and $\nu(C\text{-}N)_{str}$, respectively, indicating presence of amine group. Upon combination, shifting of $\nu(O\text{-}H)_{str}$ to 3500 cm^{-1} was observed with reduction of intensity. Further, the peak intensity of $\nu(O\text{-}H)_{def}$ was also reduced [18]. In both Sh-Gly and Sh-Gly-AA, the peak intensity of carbonyl functional group becomes more prominent with the introduction of glycine/acrylic acid to the moiety. On the other hand, the intensity of $\nu(O\text{-}H)_{str}$ observed at 3450 cm^{-1} in Sh-Gly-AA with reduced intensity.

Thermogravimetric analysis: Thermogravimetric analysis of both shellac and Sh-Gly-AA is furnished in Fig. 3. Shellac shows a gradual weight loss in the temperature range 350-450 °C attributed mostly to breaking of polymeric linkage (ester) in the molecule. Sh-Gly-AA shows a rapid weight loss and the corresponding DTA curve (Fig. 4), shows a number of endothermic and exothermic peaks within the range 50-500 °C indicating that the chemical modification of shellac leads to rearrangement in the molecular structure and hence induces instability in molecule. The inflection at 55 °C refers to the melting point of shellac [19]. Shellac contains a number of hydroxyl and carboxylic groups that can self-polymerized to produce ester linkage in the shellac structure. Increasing temperature above 300 °C resulted in decomposition reactions. The DTA of Sh-Gly-AA shows inflection at 250, 330 and 400 °C, which are the characteristic peaks of glycine molecule [20].

From the thermogravimetric analysis, it is possible to evaluate kinetic parameters that can be helpful for structural interpretation and material fabrication technology required for high end applications [21,22]. In the present investigation, we evaluated the kinetics parameters by inflection method, *i.e.*, by measuring weight fraction of decomposition/conversion [23]. Here, various model-free and model-fitting methods were taken into account for the computation of kinetic parameters [24]. Two such different models *i.e.*, (i) Coats-Redfern (CR) - a model-fitting method and (ii) Kissinger-Akahira-Sonuse (KAS) - a model-free method, were chosen for the kinetic analysis.

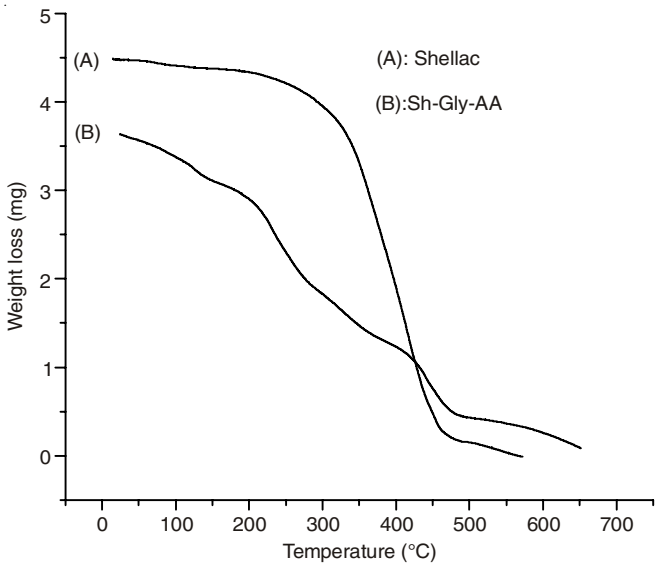


Fig. 3. Thermogravimetric curve for (A): Shellac and (B): Sh-Gly-AA showing the thermal degradation pattern of the material

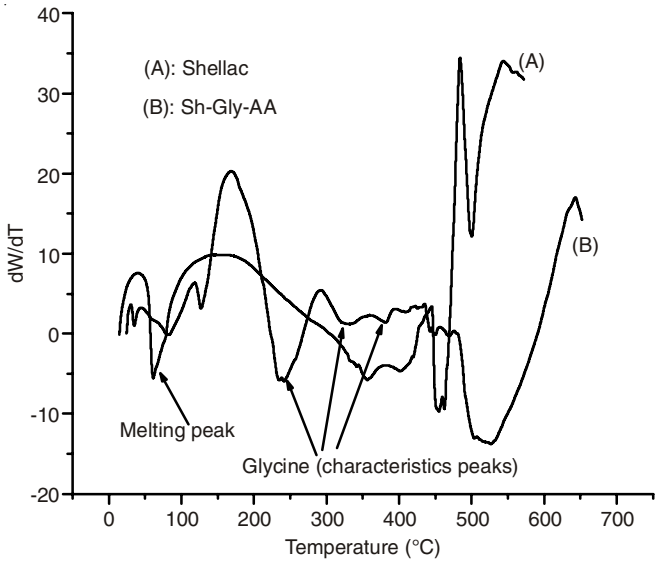


Fig. 4. Differential thermal analysis (DTA) of (A): Shellac and (B): Sh-Gly-AA

Computation of kinetics parameters using Coats-Redfern and Kissinger-Akahira-Sonuse models are initiated from the general expression for Arrhenius equation which can be expressed as [23]:

$$k = A \times e^{(-E/RT)} \quad (1)$$

where, 'k' is the reaction rate constant, 'A' is the pre-exponential factor, 'R' is the molar gas constant and 'E' denotes the activation energy.

The fundamental rate equation for kinetic studies can be expressed as:

$$dx/dt = A \times f(x)e^{(-E/RT)} \quad (2)$$

where, 'x' denotes the fraction of decomposition.

Further, for a non-isothermal method, the differential form of rate law can be expressed as [24]:

$$dx/dT = (A/\beta) \times [f(x) \times e^{-E/RT}] \quad (3)$$

where, β is the constant heating rate and T denotes the temperature.

'Coats-Redfern' is an integral method, which assumes various order of reaction and compares the linearity in each case to select the correct order. Coats-Redfern method basically uses the asymptotic series expansion for approximating the exponential integral. The logarithmic expression for Coats-Redfern model can be represented as [24]:

$$\ln [\ln (1-x)/T^2] = \ln [AR/\beta E] - E/RT \quad (4)$$

where, β denotes the heating rate. The slope of the curve $\ln [-\ln(1-x)/T^2]$ *vs.* 1/T should yield the value (-E/R) from which activation energy 'E' can be computed.

'Kissinger-Akahira-Sonuse' represents integral isoconversional technique, which can be helpful in calculation of activation energy. The logarithmic form of Kissinger-Akahira-Sonuse model can be written as [24]:

$$\ln (\beta/T^2) = \ln [AR/Eg(x)] - E/RT \quad (5)$$

From the above equation, it is clear that for constant x, the plot of $\ln(\beta/T^2)$ *vs.* 1/T should yield a straight line and the activation energy can be evaluated from the slope of the curve.

Hence, Table-1 enlists the various thermodynamic parameters obtained by using the models. Fig. 5 shows the graphical representation of Kissinger-Akahira-Sonuse model for Sh-Gly-AA. The positive value of ΔG in Table-1 indicates that the reaction involved in the decomposition of both shellac and Sh-Gly-AA were not spontaneous in nature. Again, the activation energies were also not equal to enthalpies of activation thus suggesting that the materials did not remain entirely in condensed phase in the decomposition range of study [23]. The values of ΔS, ΔH and ΔG using Coats-Redfern model for shellac were found to be 3.67 J K^{-1} mol^{-1}, 15.74 kJ mol^{-1} and 13.82 kJ mol^{-1}, respectively; whereas, for Sh-Gly-AA, the values were 6.55 J K^{-1} mol^{-1}, 396.86 kJ mol^{-1} and 396.34 kJ mol^{-1}. Analysis of these results indicated that the kinetics and thermodynamic parameters underwent significant changes only over small range of decomposition temperature where absorption of energy could lead to various structural changes in the materials due to decomposition/elimination of small molecules from the matrix. Study of these preliminary data

TABLE-1
EVALUATION OF KINETIC PARAMETERS FOR SHELLAC AND Sh-Gly-AA USING CR AND KAS MATHEMATICAL MODELS

Material	Models	Temp. (K)	E (kJ mol^{-1})	A (s^{-1})	r^2	ΔS (J K^{-1} mol^{-1})	ΔH (kJ mol^{-1})	ΔG (kJ mol^{-1})
Shellac	CR	287-573	14.1	153.4	0.9351			
	CR	573-673	159.9	3.4×10^{21}	0.9646			
	CR	287-773	20.1	23.0	0.9037	3.67	15.74	13.82
	KAS	287-773	8.0					
Sh-Gly-AA	CR	297-924	401.2	1.28	0.9608	6.55	396.8	396.3
	KAS	297-924	8.57					

CR = Coats-Redfern; KAS = Kissinger-Akahira-Sonuse

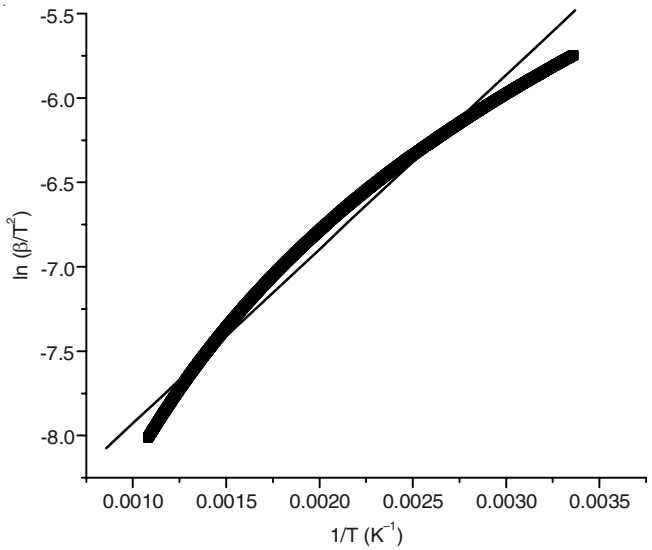


Fig. 5. Application of Kissinger-Akahira-Sonuse model for the determination of kinetic parameters for Sh-Gly-AA

can be helpful in further carrying out investigation involving material property and efficiency in various physiological environment.

Study of morphological features: The scanning electron micrograph (Fig. 6), illustrate morphological feature of shellac and Sh-Gly-AA. Fig. 6A shows the shellac surface layers which may be formed due to the chain-to-chain ester linkage in the matrix [25]. Incorporation of glycine changes the surface morphology in a manner that signifies the presence bi-pyramidal form of glycine which is clearly visible in Fig. 6C only at higher resolution [22]. Modification of shellac could result in breaking of ester linkage and, therefore, resulted in new structural features and flexibility that could attract solvent molecules towards the matrix [26,27]. Further, the presence of acrylic acid in the moiety could facilitate intermolecular and/or intra-molecular hydrogen bonding between various functional group units present in modified shellac core resulting in formation of improved surface morphological feature as shown in Fig. 6D.

Study of controlled release of 5-amino salicylic acid: The new material was tested for controlled release of 5-amino salicylic acid, a model drug used for colon specific diseases. For this, tablets were prepared by direct compression of composite material (Sh-Gly-AA) with the powder mixture of 5-amino salicylic acid, lactose and magnesium stearate using tablet making machine. The tablet weight was 80-100 mg and contains 85 % of drug and 1 % magnesium stearate as lubricant. Lactose and polymeric materials were in equal ratio (total 14 % of tablet weight). An average mean of three dissolution test data were computed for final result.

The *in vitro* release of 5-amino salicylic acid was done at various pH of the medium and the result is illustrated in Fig. 7. The cumulative drug release pattern from the material varies when the percentage of acrylic acid content varies from 2 to 6 mol %. More amount of drug loading and release is possible with increasing concentration of acrylic acid in the matrix. It is possible that acrylic acid favours higher cross-linking in the material at higher concentration for which more quantity of drug entrapment in the moiety could be possible. It was observed that very little amount of 5-amino salicylic acid could be release from material at low pH of the medium. However, almost 92 % of drug could be released when pH of the medium increases to 8.2. This could be attributed to water uptake by cross-linked polymer chains thus facilitating expansion of polymeric network structure resulting in chain relaxation and swelling of the material [28]. Hence, this process controls the release of drug molecule from polymeric network structure. Further, the release kinetics of 5-amino salicylic acid from the polymeric material was studied using Fick's model equation [29]:

$$M_t/M_e = k\, t^n \qquad (6)$$

where, M_t and M_e are the amount of drug released at time 't' and in the equilibrium, respectively. 'k' is a characteristic constant of the system and 'n' an exponent related to the kind of transport of the buffer solutions. The value of n = 0.5 indicates a Fickian diffusion process; but 0.5 < n < 1 indicates non-Fickian or anomalous diffusion. In special case, in which n = 1, the transport mechanism is named as Type II diffusion. In present investigation, the plot of ln (M_t/M_e) *vs*. ln t shows a

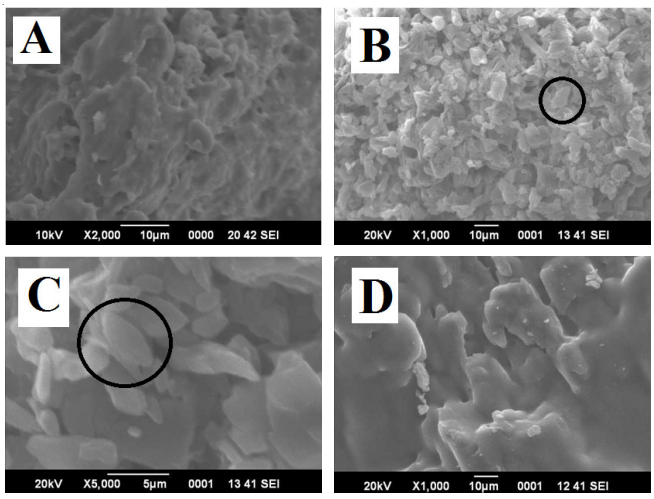


Fig. 6. Scanning electron micrograph of (A): Shellac, (B): Sh-Gly (C): Sh-Gly (at high resolution) and (D): Sh-Gly-AA; The circle shows the presence of glycine in the matrix

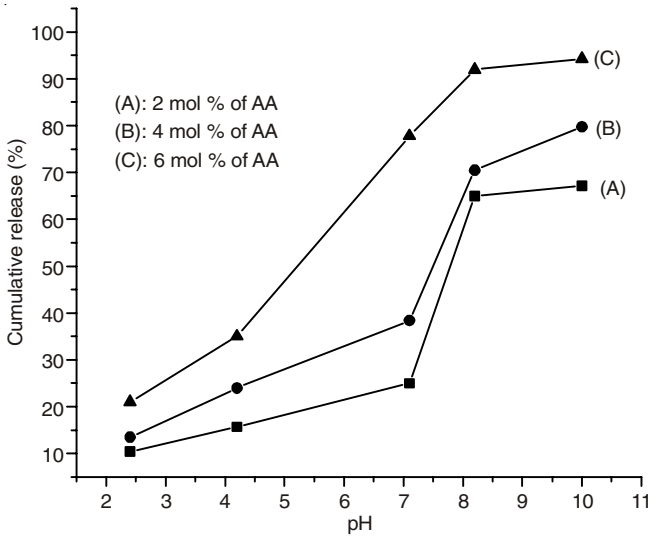


Fig. 7. Plot of pH *vs*. cumulative release of model drug with variation of acrylic acid (AA) content

linearity and the values of 'n' and 'k' were computed from the slope and the intercept, respectively. In present case, the calculated values of exponent 'n' lies between 0.8 to 0.9 indicating that erosion of polymeric material is the major factor which leads to release of entrapped drug molecules from the material [29,30].

Conclusion

In conclusion, a new pH responsive polymeric material was prepared by chemical modification of shellac using glycine and acrylic acid. The FTIR spectra of the material shows characteristic peaks of shellac and glycine indicating chemical modification of shellac. The thermal stability and kinetics of decomposition of the material were evaluated using Coats-Redfern and Kissinger-Akahira-Sonuse models. The calculated value of ΔG shows non-spontaneous nature of decomposition of both shellac and Sh-Gly-AA. Computation of activation energies and enthalpies of activation suggested that the materials did not remain in condensed phase over total decomposition range under study. Modification of shellac resulted new structural features and flexibility that could be helpful in controlled release of drugs in a buffer medium. The newly developed shellac based material can also find diverse applications in pharmaceutical and biomedical field of research with further studies in this direction.

ACKNOWLEDGEMENTS

The research is funded by Department of Science and Technology (DST), New Delhi, India vide grant no. SR/S1/PC-24/2009.

REFERENCES

1. N. Mohamad, M.C.I. Mohd Amin, M. Pandey, N. Ahmad and N.F. Rajab, *Carbohydr. Polym.*, **114**, 312 (2014); http://dx.doi.org/10.1016/j.carbpol.2014.08.025.
2. J.-Y. Lai, *Mater. Sci. Eng. C*, **51**, 28 (2015); http://dx.doi.org/10.1016/j.msec.2015.02.021.
3. S. Lin, Y. Guo, X. Li and Y. Liu, *Mater. Lett.*, **152**, 102 (2015); http://dx.doi.org/10.1016/j.matlet.2015.03.099.
4. Z. Zhang, L. Chen, C. Zhao, Y. Bai, M. Deng, H. Shan, X. Zhuang, X. Chen and X. Jing, *Polymer*, **52**, 676 (2011); http://dx.doi.org/10.1016/j.polymer.2010.12.048.
5. S. Mirdarikvande, L. Mansouri, M. Alahyari, H. Sadeghi, H. Shasavari and F. Khani, *Biosci. Biotechnol. Res. Asia*, **11**, 67 (2014); http://dx.doi.org/10.13005/bbra/1234.
6. T. Gyenes, V. Torma, B. Gyarmati and M. Zrínyi, *Acta Biomater.*, **4**, 733 (2008); http://dx.doi.org/10.1016/j.actbio.2007.12.004.
7. W.E. Hennink, O. Franssen, W.N.E. van Dijk-Wolthuis and H. Talsma, *J. Control. Release*, **48**, 107 (1997); http://dx.doi.org/10.1016/S0168-3659(97)00047-3.
8. C.K. Simi and T. Emilia Abraham, *Eur. J. Pharm. Sci.*, **32**, 17 (2007); http://dx.doi.org/10.1016/j.ejps.2007.05.003.
9. E.R. Pérez, D.M. García-Cruz, M.C. Araque-Monros, U. Gomez-Pinedo, M.M. Pradas and J.L. Escobar-Ivirico, *J. Bioact. Compat. Polym.*, **28**, 50 (2013); http://dx.doi.org/10.1177/0883911512469710.
10. R.Y. Tam, M.J. Cooke and M.S. Shoichet, *J. Mater. Chem.*, **22**, 19402 (2012); http://dx.doi.org/10.1039/c2jm33680d.
11. S. Rothemund, T.B. Aigner, A. Iturmendi, M. Rigau, B. Husár, F. Hildner, E. Oberbauer, M. Prambauer, G. Olawale, R. Forstner, R. Liska, K.R. Schröder, O. Brüggemann and I. Teasdale, *Macromol. Biosci.*, **15**, 351 (2015); http://dx.doi.org/10.1002/mabi.201400390.
12. S.G. Roy and P. De, *Polymer*, **55**, 5425 (2014); http://dx.doi.org/10.1016/j.polymer.2014.08.072.
13. Y. Farag and C.S. Leopold, *Eur. J. Pharm. Sci.*, **42**, 400 (2011); http://dx.doi.org/10.1016/j.ejps.2011.01.006.
14. J. Al-Gousous, M. Penning, P. Langguth, J. Al-Gousous, M. Penning and P. Langguth, *Int. J. Pharm.*, **484**, 283 (2015); http://dx.doi.org/10.1016/j.ijpharm.2014.12.060.
15. V. Ravi, Siddaramaiah and T.M. Pramod Kumar, *J. Mater. Sci. Mater. Med.*, **19**, 2131 (2008); http://dx.doi.org/10.1007/s10856-007-3155-x.
16. R.K. Dey, G.S. Tiwary, T. Patnaik and U. Jha, *Polym. Bull.*, **66**, 583 (2011); http://dx.doi.org/10.1007/s00289-010-0294-x.
17. J. Bae and J.W. Park, *Trop. J. Pharm. Res.*, **14**, 363 (2015); http://dx.doi.org/10.4314/tjpr.v14i3.2.
18. S. Limmatvapirat, C. Limmatvapirat, S. Puttipipatkhachorn, J. Nuntanid and M. Luangtana-anan, *Eur. J. Pharm. Biopharm.*, **67**, 690 (2007); http://dx.doi.org/10.1016/j.ejpb.2007.04.008.
19. S. Limmatvapirat, C. Limmatvapirat, S. Puttipipatkhachorn, J. Nunthanid, M. Luangtana-Anan and P. Sriamornsak, *Eur. J. Pharm. Biopharm.*, **69**, 1004 (2008); http://dx.doi.org/10.1016/j.ejpb.2008.01.027.
20. J. Li, Z. Wang, X. Yang, L. Hu, Y. Liu and C. Wang, *J. Anal. Appl. Pyrolysis*, **80**, 247 (2007); http://dx.doi.org/10.1016/j.jaap.2007.03.001.
21. G.G. Mohamed, H.F. Abd El-Halim, M.M.I. El-Dessouky and W.H. Mahmoud, *J. Mol. Struct.*, **999**, 29 (2011); http://dx.doi.org/10.1016/j.molstruc.2011.05.018.
22. M. Rabesiaka, M. Sghaier, B. Fraisse, C. Porte, J.-L. Havet and E. Dichi, *J. Cryst. Growth*, **312**, 1860 (2010); http://dx.doi.org/10.1016/j.jcrysgro.2010.03.011.
23. A.S. Abu-Bakar and K.A.M. Moinuddin, Effects of Variation in Heating Rate, Sample Mass and Nitrogen Flow on Chemical Kinetics for Pyrolysis, 18th Australasian Fluid Mechanics Conference Launceston, Australia 3-7 December 2012.
24. E. Apaydin-Varol, S. Polat and A.E. Putun, *Thermal Sci.*, **18**, 833 (2014); http://dx.doi.org/10.2298/TSCI1403833A.
25. S. Limmatvapirat, D. Panchapornpon, C. Limmatvapirat, J. Nunthanid, M. Luangtana-Anan and S. Puttipipatkhachorn, *Eur. J. Pharm. Biopharm.*, **70**, 335 (2008); http://dx.doi.org/10.1016/j.ejpb.2008.03.002.
26. J. Berger, M. Reist, J.M. Mayer, O. Felt, N.A. Peppas and R. Gurny, *Eur. J. Pharm. Biopharm.*, **57**, 19 (2004); http://dx.doi.org/10.1016/S0939-6411(03)00161-9.
27. D. Phan The, F. Debeaufort, D. Luu and A. Voilley, *J. Membr. Sci.*, **325**, 277 (2008); http://dx.doi.org/10.1016/j.memsci.2008.07.052.
28. S.A. Agnihotri and T.M. Aminabhavi, *J. Control. Release*, **96**, 245 (2004); http://dx.doi.org/10.1016/j.jconrel.2004.01.025.
29. B.M. Vogel and S.K. Mallapragada, *Biomaterials*, **26**, 721 (2005); http://dx.doi.org/10.1016/j.biomaterials.2004.03.024.
30. L. Serra, J. Doménech and N.A. Peppas, *Biomaterials*, **27**, 5440 (2006); http://dx.doi.org/10.1016/j.biomaterials.2006.06.011.