RESEARCH ARTICLE

Study on Natural Gums and Resins as Release Retarding Agents in Development of Sustained Release Matrix Tablets of Didanosine

Y Indira Muzib[1*], K Swetha[1], YR Ambedkar[2]

[1]*Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam (Women's University), Tirupati, Andhra Pradesh, India.*
[2]*College of Veterinary Science, Sri Venkateswara Veterinary Univesity, Vizianagaram, Andhra Pradesh, India.*

Received: 09th October, 2023; Revised: 08th December, 2023; Accepted: 23rd April, 2024; Available Online: 25th June, 2024

ABSTRACT

Didanosine is an anti-retroviral drug which helpful in preventing human immunodeficiency virus (HIV) from multiplication in the body. This drug has a relatively short half-life and low absolute bioavailability and requires frequent dosing. So to avoid this frequent dosing and to improve the patient's compliance, the development of sustained-release tablets is necessary. Natural gums and resins play an important role in retarding drug release. Didanosine extended-release matrix formulations developed with wet granulation using gum kondagogu, guar gum, gum olibanum, and olibanum resin, and evaluated for pre and post-compression parameters. The outcome of all evaluation tests is reached IP specifications. Formulations with kondagogu F1-F3 failed to extend the drug release. F4-F6 was formulated with gum kondagogu and guar gum, in which F4 prolonged the release up to 12 hours with 98.23%. The formulations F7 with olibanum resin release 96.13%, and F10 with gum olibanum releases 93.15% drug at the end of 12 hours. The conclusion from the study was that natural polymers could be used to enhance drug release for an extended period.

Keywords: Didanosine, Sustained release, Natural gums, Resins, Matrix tablets.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.2.01

How to cite this article: Muzib YI, Swetha K, Ambedkar YR. Study on Natural Gums and Resins as Release Retarding Agents in Development of Sustained Release Matrix Tablets of Didanosine. International Journal of Drug Delivery Technology. 2024;14(2):619-624.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Oral controlled or sustained-release dosage forms are more convenient to administer the patients. To reduce the dosing frequency, to extend the duration of action, to maintain plasma levels and to diminish adverse effects sustained-release dosage forms are necessary.[1-3] For orally administered systems, the bulk size of the dose and treatment duration plays a key role in the development of sustained-release dosage forms.[4] Chronic diseases require long treatment, which results in the accumulation of drugs in the body, leading to side effects. This also makes the selection of SR formulations. The drug is uniformly disseminated throughout a polymer matrix in a matrix device to achieve prolonged release. The drug in the matrix device dissolves first and then diffuses out of the matrix when it is in the outer layer exposed to the dissolving fluid and releases the drug in a sustained manner.[5-8] Hydrophilic swellable polymers are abundantly available, biodegradable, biocompatible, non-toxic, and economical. They are frequently employed to regulate the drug release from extended-release matrix tablets. When the polymer matrix comes in contact with the dissolution fluid, hydrophilic polymer get moisturized and forms a hydrogel plug which serves as a barrier and intervenes with water penetration into the tablet to retard the drug release quickly. The thickness of the layer determines the drug molecule diffusion path through the polymer and dissolving media.[9] Gums like xantham gum, karaya gum, guar gum, gum olibanum and resin such as olibanum resin have been proven to be beneficial for prolonged release due to their hydrophilic property.[10-14] Didanosine was chosen in this study as it is a first-line anti-retroviral drug used in the treatment of human immunodeficiency virus (HIV) infections and also it is administered in multiple doses in conventional therapy due its short biological half-life. Didanosine matrix tablets were formulated with synthetic polymers[15] and natural polymers. In the present work, gum kondagogu (GK), guar gum (GG), olibanum resin (OR), gum olibanum (GO) are used as release retarding agents.

**Author for Correspondence: yindira1415@gmail.com*

MATERIALS AND METHODS

Didanosine procured from Aurobindo Pharma Ltd, Hyd. Gum gondagogu, gum olbinum and guar gum was from Girijan Cooperative Corporation Ltd, Vishakapatnam, as a gift sample. Other chemicals purchased from SD Fine Chemical Ltd.

Formulation of Didanosine Matrix Tablets

FTIR study

The fourier-transform infrared (FTIR) method was used to check the interaction between drugs and polymers with an FTIR spectrometer (FTIR, Shimadzu, Japan).

Wet granulation technique

Wet granulation was applied in the preparation of didanosine (DDI) sustained release (SR) formulations. Various proportions of selected polymers gum kondagogu, guar gum, olibanum resin, gum olibanum were utilized in the preparation to know the release modulating property. The composition of didanosine matrix tablets is given in Table 1. All the powders passed through a sieve and added granulating agent with thorough mixing. Then obtained wet dough was screened through no. 16 mesh. The obtained granules were dried at 50°C for 2 hours in hot air oven. Further talc and magnesium stearate were added as a glidant and lubricant. The dried granules were subjected to various parameters and were compressed with a weight of 250 mg.

Evaluation of Pre-compression Parameters[16]

The DDI granules were formulated with various natural gums and resins and were evaluated for various pre-compression tests. Flow property was determined by measuring the angle of repose, Carr's index, and Hausner's ratio. Tapped density bulk density was measured by cylinder method. Moisture content and loss on drying were measured by taking 1-gm of granules in a petri dish and, keeping in the oven at 105°C and drying till it reached constant weight. By taking the weight of granules before and after drying percentage of moisture content and loss on drying was calculated.

Post-compression Parameters of Tablets[17]

The post-compression tests of tablets were determined according to IP specifications. The naked eye tested the general appearance. Vernier calipers used to determine the thickness of tablet (Linker, Mumbai). Monsanto hardness tester (Shimadzu, Mumbai) was used to determine the hardness of tablets, and Roche friability (Roche, Mumbai) was used for the friability test. Variation in the weight was performed as per IP specifications and percent deviation was calculated. After weighing 20 tablets individually, taking the average weight of all tablets and individual weight percent deviation in weight was calculated. Drug content uniformity was determined by measuring the absorbance of standard and samples at 248 nm by UV-visible spectrophotometer (Shimadzu corporation, Mumbai).

Swelling or water uptake studies

Swelling studies were determined by the weight gain method. The swelling behavior of the optimized tablets was studied. The percent increase in weight due to absorbed liquid was estimated at each point by the following equation:

$$\%\text{Weight change} = \frac{W_1 - W_0}{W_1} \times 100$$

Where, W_1-Final weight of tablet, W_0- Initial weight of tablet

In-vitro Drug Release and Kinetic Analysis Studies

The USP-XXII dissolution apparatus with a paddle type at a rotational speed of 50 rpm at 37 ± 0.5°C was used to conduct the dissolution studies. The percentage of drug release at different time intervals was determined with 900 mL of pH 0.1N HCl, phosphate buffer pH 7.2 was used as dissolution media for the first 2 hours and continued with a further 12 hours. The collected samples were analyzed at 248 nm using a UV-visible spectrophotometer after filtering through 0.45 µ membrane and cumulative percent drug release was calculated. The obtained results were inserted in zero, First order, Higuchi, Koresmayer-Peppas equations to know drug release mechanism from polymer matrix.[18]

Table 1: Composition of didanosine matrix formulations

Formulation code	*Drug*	*Gum kondagogu*	*Guar gum*	*Olibanum resin*	*Gum Olibanum*	*Avicel*	*Starch*	*Talc*	*Magnesium stearate*	*Total weight*
F1	100	75	-	-	-	42.5	25	5	2.5	250
F2	100	80	-	-	-	37.5	25	5	2.5	250
F3	100	100	-	-	-	17.5	25	5	2.5	250
F4	100	37.5	37.5	-	-	42.5	25	5	2.5	250
F5	100	40	40	-	-	37.5	25	5	2.5	250
F6	100	50	50	-	-	17.5	25	5	2.5	250
F7	100	-	-	75	-	42.5	25	5	2.5	250
F8	100	-	-	80	-	37.5	25	5	2.5	250
F9	100	-	-	100	-	17.5	25	5	2.5	250
F10	100	-	-	-	75	42.5	25	5	2.5	250
F11	100	-	-	-	80	37.5	25	5	2.5	250
F12	100	-	-	-	100	17.5	25	5	2.5	250

Quantity (mg) present per each Matrix tablet

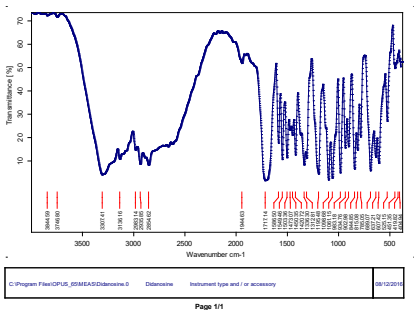

Figure 1: FTIR spectra of didanosine

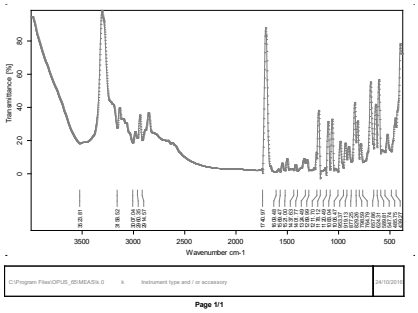

Figure 2: FTIR spectra of GK

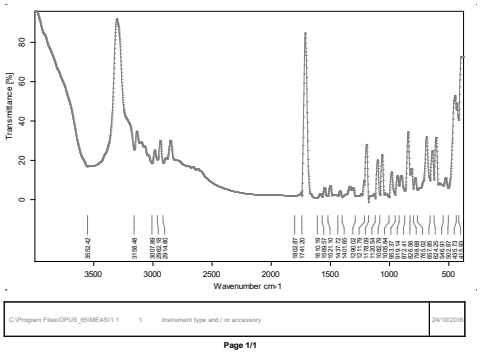

Figure 3: FTIR spectra of GG

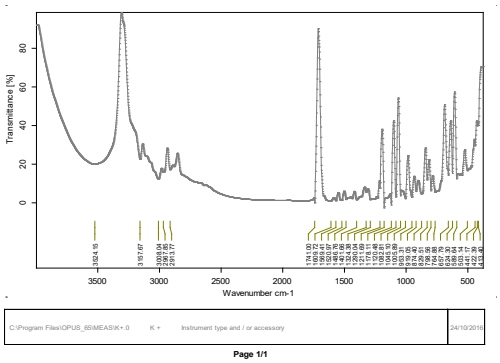

Figure 4: FTIR spectra of F4 matrix tablet

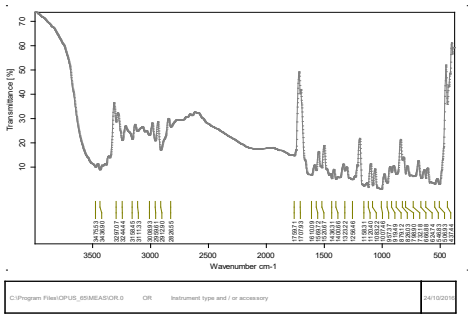

Figure 5: FTIR spectra OR

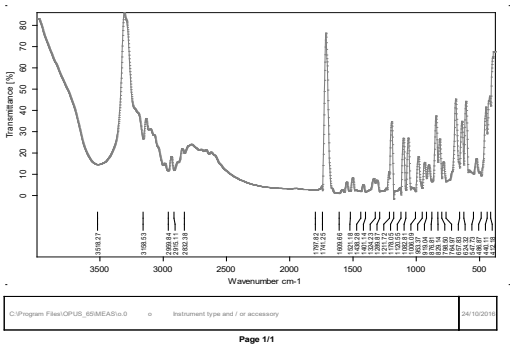

Figure 6: FTIR spectra of F7 matrix tablets

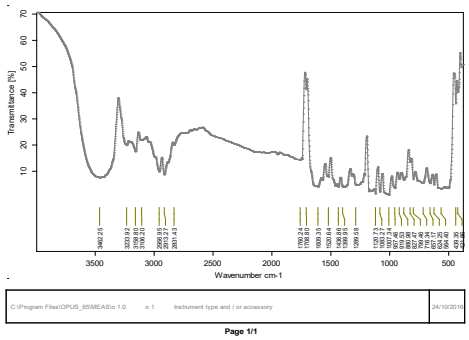

Figure 7: FTIR spectra of GO

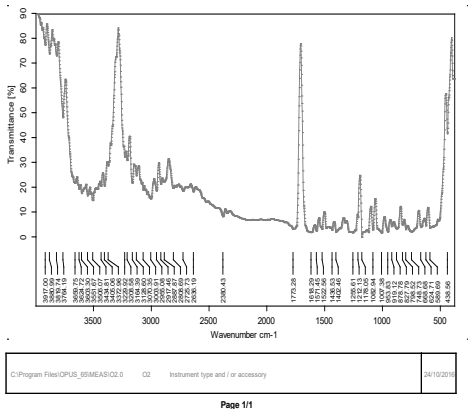

Figure 8: FTIR spectra of F10 matrix tablet

RESULTS AND DISCUSSION

The FTIR studies were conducted for optimized formulations of didanosine matrix tablets with a frequency range of 4000 to 400 cm^{-1}. Results reveal the compatibility between drug and polymer as the peaks appear as separate entities which is clearly shown in the spectra (Figures 1-8). The vibration frequencies of C=O stretching vibration were merged at 1717.14 cm^{-1} for pure didanosine drug. For the F4 formulation, the drug peak was found to be at 1714 cm^{-1} for F7 formulation drug peak was found to be

Table 2: Evaluation of didanosine matrix granules

Formulation	*Angle of repose (Θ)*	*Bulk density (g/cm^3)*	*Tapped density (g/cm^3)*	*Compressibility index (%)*	*Hausner's ratio*	*Drug content (%)*	*Loss on drying (%)*	*Moisture content (%)*
F1	28.10 ± 0.16	0.45 ± 0.015	0.57 ± 0.02	13.05 ± 0.44	1.26 ± 0.04	95.13 ± 0.03	3.1 ± 0.45	8.6 ± 0.43
F2	36.53 ± 0.32	0.53 ± 0.016	0.56 ± 0.013	7.69 ± 0.11	1.16 ± 0.012	90.14 ± 0.15	8.7 ± 0.036	4.3 ± 0.34
F3	26.15 ± 0.23	0.46 ± 0.013	0.52 ± 0.07	1.88 ± 0.13	1.13 ± 0.14	97.55 ± 0.02	7.5 ± 0.13	7.2 ± 0.15
F4	29.48 ± 0.73	0.45 ± 0.02	0.58 ± 0.02	6.25 ± 0.12	1.06 ± 0.01	93.12 ± 0.08	9.5 ± 0.15	8.5 ± 0.17
F5	26.32 ± 0.37	0.52 ± 0.015	0.56 ± 0.01	7.14 ± 0.16	1.07 ± 0.02	99.13 ± 0.05	4.7 ± 0.34	8.1 ± 0.54
F6	27.49 ± 0.85	0.51 ± 0.01	0.53 ± 0.013	5.66 ± 0.88	1.16 ± 0.17	109.14 ± 0.17	9.2 ± 0.032	8.3 ± 0.15
F7	27.12 ± 0.40	0.46 ± 0.01	0.48 ± 0.03	9.71 ± 0.12	1.02 ± 0.02	102.10 ± 0.4	3.1 ± 0.45	8.6 ± 0.043
F8	28.61 ± 0.73	0.59 ± 0.05	0.49 ± 0.04	2.04 ± 0.17	1.16 ± 0.015	91.18 ± 0.7	8.2 ± 0.10	8.8 ± 0.01
F9	25.62 ± 0.19	0.56 ± 0.02	0.57 ± 0.01	14.81 ± 0.39	1.19 ± 0.015	96.13 ± 0.2	9.2 ± 0.32	8.3 ± 0.013
F10	29.22 ± 0.59	0.42 ± 0.07	0.59 ± 0.02	8.61 ± 0.64	1.01 ± 0.02	99.03 ± 0.7	8.2 ± 0.10	8.6 ± 0.43
F11	37.15 ± 0.35	0.52 ± 0.05	0.55 ± 0.01	1.88 ± 0.32	1.19 ± 0.02	105.13 ± 0.1	3.2 ± 0.45	9.0 ± 0.011
F12	24.19 ± 0.17	0.47 ± 0.06	0.51 ± 0.07	12.34 ± 0.15	1.06 ± 0.06	97.02 ± 0.6	5.9 ± 0.67	9.2 ± 0.14

All the values are expressed as mean ± SD, n = 3

Table 3: Post-compression parameters of matrix formulations

Formulation	*Weight variation (mg)*	*Hardness (mm)*	*Thickness (kg/cm^2)*	*Friability (%)*	*Drug content (%)*	*Swelling index (%)*
F1	248.3 ± 0.02	6.8 ± 0.013	4.1 ± 0.03	0.81 ± 0.05	99.13 ± 0.01	65.25 ± 0.02
F2	249.9 ± 0.03	6.6 ± 0.089	3.91 ± 0.04	0.78 ± 0.02	98.19 ± 0.03	87.13 ± 0.05
F3	250.7 ± 0.04	6.3 ± 0.017	4.2 ± 0.07	0.74 ± 0.06	95.01 ± 0.06	98.14 ± 0.03
F4	252.6 ± 0.01	6.5 ± 0.021	3.46 ± 0.03	0.80 ± 0.04	97.33 ± 0.07	81.08 ± 0.03
F5	250.3 ± 0.09	6.9 ± 0.024	3.95 ± 0.02	0.82 ± 0.05	99.14 ± 0.01	88.08 ± 0.03
F6	253.6 ± 0.05	6.8 ± 0.013	3.49 ± 0.03	0.79 ± 0.02	100.15 ± 0.07	90.12 ± 0.02
F7	252.7 ± 0.08	6.3 ± 0.013	4.1 ± 0.03	0.81 ± 0.05	90.18 ± 0.15	58.0.6 ± 0.13
F8	248.9 ± 0.05	7.1 ± 0.046	3.22 ± 0.06	0.83 ± 0.07	93.19 ± 0.19	82.3 ± 0.05
F9	251.1 ± 0.19	6.2 ± 0.053	3.91 ± 0.01	0.77 ± 0.01	99.10 ± 0.13	98.10 ± 0.07
F10	250.4 ± 0.02	7.0 ± 0.035	3.95 ± 0.02	0.80 ± 0.02	96.18 ± 0.14	75.06 ± 0.03
F11	250.7 ± 0.08	6.6 ± 0.089	3.92 ± 0.01	0.78 ± 0.15	97.10 ± 0.45	89.14 ± 0.15
F12	247.9 ± 0.05	6.9 ± 0.045	4.0 ± 0.03	0.79 ± 0.14	98.17 ± 0.17	90.12 ± 0.02

All the values are expressed as mean ± SD

at 1714.25 cm^{-1} and for F10 formulation drug peak was found to be at 1773.28 cm^{-1}. Similarly, spectra of the pure drug and optimized formulations F4, F7, F10 revealed that there was no shift of characteristic absorption bands positions in the spectra.

Pre-compression Parameters

All the formulated granules (F1–F12) were evaluated for Physical properties and the results obtained were mentioned in Table 2.

The granules of proposed formulations are evaluated for angle of repose (Θ), bulk density, tapped density, compressibility index, Hausner's ratio, drug content, loss on drying, moisture content in Table 2. The values present in Table 2 shows prepared granules with various polymers have good flow properties and moisture content also present within the limits.

Table 3 represents outcome of evaluation tests which reveals that uniformity in weight variation and drug content. The hardness of tablets within the range of 6.2 ± 0.053 to 7.1 ± 0.046 kg/cm^2, and friability is between 0.74 to 0.83, which is less than the permitted range of 1%. The average thickness varied from 3.22 ± 0.06 to 4.2 ± 0.07 mm and was found to be consistent across all formulations. Formulations exhibited swelling index varied with different gums and resins.

***In-vitro* Drug Release Studies**

Didanosine was released from matrix tablets and extended maximum period of 12 hours. Analyzing the drug release from various gums and resin-based formulations, initially, F1, F2, F3 were prepared with GK. Figure 9 illustrates the active pharmaceutical ingredient release from the formulations of gum kondagogu. The majority of the drug release was identified at 6 hours, and further unable to prolong the release up to 12 hours. Therefore, GK and GG were combined in various proportions (F4, F5, F6) with increasing polymer quantity in an attempt to delay the drug release. The polymer

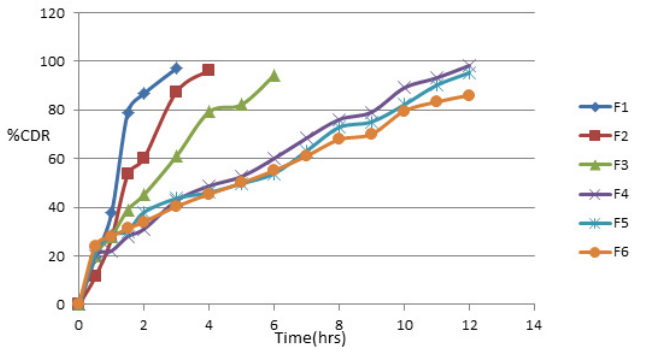

Figure 9: Percentage cumulative drug release plot of formulations with GK (F1-F3) and GK + GG (F4-F6)

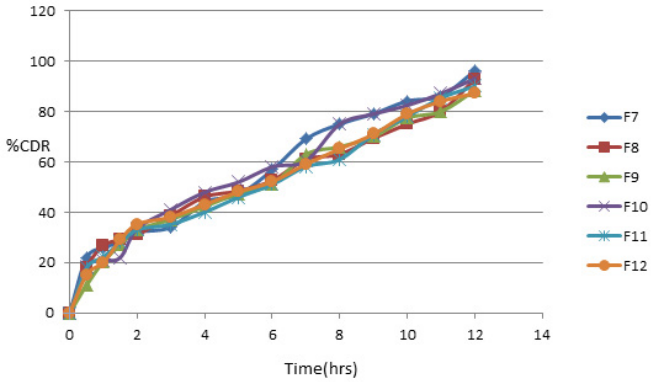

Figure 10: Percentage cumulative drug release plot of formulations with OR (F7-F9) and GO (F10-F12)

combination of (1:1) and drug F4 (drug:polymer,1:0.75) was found to exhibit a release profile of 98.23%, and the release was extended up to 12 hours. The drug release profiles of F4, F5, F6 are illustrated in Figure 9. Didanosine matrix tablets were also formulated by using olibanum resin with the ratio of drug: polymer F 7 (1:0.75), F8 (1:0.80) , F9 (1:1). In the case of F7 it showed 96.13% drug release by the end of 12th hour, and a further increase in polymer quantity Didanosine release was reduced. The drug release profiles of F7, F8, F9 were represented in Figure 10. With gum olibanum in case of F10 (drug : polymer) (1: 0.75), F11 (1:0.80) , F12 (1:1) F10 gave 93.15% drug release by the end of 12th hour and here it was observed that gum olibanum showed the similar pattern of olibanum resin, that is enhancing the amount of polymer the drug release was retarded. The release profiles were shown in Figure 10. From the four different polymers employed in the present study three formulations F4, F7 and F10 were optimized as the drug release was found to be more than 90%. The amount of drug and polymer in the matrix tablets determines the drug's emancipation. Changes in the hydrophilic gum polymer's gel strength or systemic rearrangement could be the cause of this. In gum kondagogu based tablets, rapid drug release may result from a failure to induce a sufficient consistency of hydrogel of gum kondagu.

Table 4: Release kinetics of optimized matrix tablets

Formulation code	*Release model*				
	Zero order	*First order*	*Higuchi*	*Koresmeyer-Peppas*	
	R^2	R^2	R^2	n	R^2
F4	0.973	0.842	0.983	0.544	0.972
F7	0.967	0.873	0.959	0.496	0.939
F10	0.958	0.900	0.978	0.545	0.969

The R^2 values were determined for optimized preparations (F4, F7, F10) to know the mechanism of drug release by inserting the data in various release models. The R^2 value of zero order, first order, Higuchi, Korcemayer-Peppas model was represented in Table 4. The results show that optimized matrix tablets followed zero order and Higuchi release kinetics with R^2>0.98, which demonstrates improved linearity and suggests that a diffusion process is used to release didanosine. The Korsmayer-Peppas equation describes drug release behavior from polymeric materials. The R^2, n values of F4, F7, F10 reveal the drug release combination of both diffusion and erosion. The n value of F4 less than 0.5 suggests that fickian (case 1) release, whereas for F7, F10 n value more than 0.5 but less than 0.97 indicates Non-fickian (anomalous) transport. It was found that the release rate steadily falls as the swelling index increases.

CONCLUSION

Sustained release matrix tablets of didanosine formulated utilizing matrix based technology with natural gums by wet granulation technique. Many authors reported from their studies that sustained drug delivery systems are well-proven and documented to be therapeutically superior to conventional controlled-release dosage forms. The natural gums and resins used in the present formulations were proven to be successful as release retarding agents through the obtained results, which are successful in the release of the drug up to 12 hours. The formulation prepared can be considered biocompatible and biodegradable owing to all the superior benefits of natural agents or excipients over synthetic ones. It is concluded from the obtained results that natural gums and resins could be utilized as release retardants in appropriate quantities with different combinations.

ACKNOWLEDGMENTS

The author acknowledges higher authorities of the Institute, DST CURIE and FIST centers of Sri Padmavati Mahila Visva Vidyalayam for providing facilities to carry out the work.

REFERENCES

1. Jain KK. Drug delivery systems. 1st edition. Switzerland: Humana Press; 2008.March 7: P. 1-51.
2. Lachman L, Herbert AL, Joseph LK. The theory and practice of industrial pharmacy. 3rd edition. Bombay: Varghese publishing house; 1986. P. 430-455.
3. Joseph RR, Vincent HLL. Controlled drug delivery fundamentals

and applications. 2nd edition revised and expanded. New York: Marcel Dekker Inc; 1987. P. 3-56.
4. Chien YW. Novel drug delivery system. 2nd edition revised and expanded. New York: Informa health care; 2009. P. 1-50
5. Gilbert SB, Christopher TR. Modern pharmaceutics. 3rd edition revised and expanded. New York: Marcel Dekker Inc; 1995. P. 575-608.
6. Donald LW. Handbook of pharmaceutical controlled release technology. 1st edition. New York: Marcel Dekker Inc; 2000. P. 431-460.
7. Yvonne p, Thomas R. Pharmaceutics-Drug delivering targeting. 1st edition. Pharmaceutical press; 2010. P. 85-115, 117-139.
8. Khalane L, Alkunte AT, Birajdar AR. Sustained release drug delivery system: a concise review. Terminology. 2016;4(5).
9. Khan GM. Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems. The Sciences. 2001 Sep;1(5):350-4.
10. Senapati MK, Srinatha A, Pandit JK. In Vitro Release Characteristics of Matrix Tablets: Study of Karaya Gum and Guar Gum as Release Modulators. IndianJournal of Pharmaceutical Sciences. 2006 Nov 1;68(6).**DOI**: 10.4103/0250-474X.31028
11. Krishnaiah YS, Muzib YI, Rao GS, Bhaskar P, Satyanarayana V. Studies on the development of colon targeted oral drug delivery systems for ornidazole in the treatment of amoebiasis. Drug Delivery. 2003 Jan 1;10(2):111-7.DOI: 10.1080/713840359
12. Chowdary KP, Mohapatra P, Krishna MM. Evaluation of olibanum resin as microencapsulating agent for controlled drug delivery. Indian Journal of Pharmaceutical Sciences. 2006 Jul 1;68(4).
13. Muzib YI, Kurri PS. Formulation and evaluation of gum olibanum-based sustained release matrix tablets of ambroxol hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences. 2011
14. Sánchez-Lafuente C, Faucci MT, Fernández-Arévalo M, Álvarez-Fuentes J, RabascoAM, Mura P. Development of sustained release matrix tablets of didanosine containing methacrylic and ethylcellulose polymers. International Journal of Pharmaceutics. 2002 Mar 2;234(1-2):213-21.DOI: 10.1016/s0378-5173(01)00962-0
15. Soumya P, Rao NR, Revathi K, Chawda B. Design and development of oral sustained release matrix tablets of didanosine using natural polymer blend. Journal of Chemical and Pharmaceutical Research. 2013;5(12):1398-408.
16. Dada Kodalkar, Ajit Kulkarni , Birendra Shrivastav , Harshal Tare.Preparation, Characterization of Bacterial Cellulose and Chlordiazepoxide Tablets for Oral Drug Delivery. International Journal of Pharmaceutical Quality Assurance, Volume 13 Issue 4, October - December 2022 408-412: DOI: 10.25258/ijpqa.13.4.11
17. Rutu H Patel, Harsh J Trivedi, Kunal N Patel , Madhabhai M Patel. Design, Development and Optimization of Pulsatile Core in Cup Tablets of Naproxen. International Journal of Drug Delivery Technology 2017; 7(3); 220-233 doi: 10.25258/ijddt.v7i03.9565
18. Costa P, Lobo JM. Modeling and comparison of dissolution profiles. European Journal Of Pharmaceutical Sciences. 2001 May 1;13(2):123-33. https://doi.org/10.1016/S0928-0987(01)00095-1