ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Development, optimization and In vitro evaluation of sintered floating tablets of Antibacterial drug

Rajesh Akki*, Angala parameswari S, Kothapalli Bannoth Chandra sekhar

Jawaharlal Nehru Technological University Ananatapur, Ananthapuramu - 515002, Andhra Pradesh, India

Article History:

Received on: 02 Jan 2020
Revised on: 07 Feb 2020
Accepted on: 03 Mar 2020

Keywords:

Amoxicillin Trihydrate,
Carnauba wax,
Gastro retentive,
Thermal sintering

ABSTRACT

Floating tablets prolongs drug residence, enhance bioavailability and facilitate effective eradication of helicobacter pylori includes local delivery of antibiotic in stomach. The goal of the existing research changed into to formulate thermally sintered floating Tablets of Amoxicillin Trihydrate, and to test sintering effect on release of drug and floating. A hydrophobic polymer, Carnauba wax, is determined to delay the release of drug as a sintered polymer. Formulations had been organized via granulation technique and had been evaluated through in vitro research such as hardness, friability, uniformity of weight, percentage drug content, buoyancy time, dissolution and release mechanism. Optimization was based on buoyancy time and in vitro release. Hardness ranged from 4-6 kg/cm^2. Friability, drug content and weight variation passed USP requirements. Buoyancy time of all tablets was below 3 min and tablet remained floating throughout the study. Effects showed that temperature to sinter and exposure time significantly motivated buoyancy, in addition to dissolution characteristics. Sintering improved floating properties, general time of floating was extended and retarded release of medicament. Robust sintered components (sintering temperature 50°C and time of exposure 4 h became selected, primarily based on retarding character. The formulations characterised with FTIR studies and no interplay become determined between the drug and the polymer.

*Corresponding Author

Name: Rajesh Akki
Phone: 9908451213
Email: rajuph111@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2102

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Warm sintering is a technique for warming "polymer in a sintering heater beneath its liquefying point (strong state sintering) until its particles cling to one another". In this procedure, particles of polymer will experience combination or arrangement of bonds welded in between every molecule. Sintering a compelling when procedure decreases the porosity and upgrades mechanical quality of powder particles. Sintering happens at raised temperature and includes predominantly three rule steps; joining the neighbouring particles named as neck development, arrangement of channels interconnecting pores named densification pursued by arrangement of circular state of particles that will in general stream into the pores inside it because of the distinction between fume pressure and cross sectional territory of the neck pore's. Phases of sintering are holding of particles and at last in expulsion of inside porosity. Causing outside shrinkage and accomplishment of attractive physical properties (Hornsby and Maxwell, 1992).

The sintering strategy includes the introduction of the measurement structure at particular temperature which mollifies polymer network and prompts development of bonds welded. The medication molecule captured in grid framed and outcomes in controlled arrival of dynamic fixing. Notwithstanding, strategy might be applied uniquely to medications that are temperature safe on presentation which constraining component for some medications debase at raised temperatures (Cohen *et al.*, 1984; German, 1996).

Pellets were fused with carnauba wax utilizing warm sintering method. Incorporation of wax emulsified from carnauba didn't control arrival of theophylline in excess of 3h, while enhanced temperature and length of exposure for sintering the pellets controlled arrival of the medication for a 12 h time (Singh *et al.*, 2007). In this Present study Amoxicillin trihydrate was chosen as model drug. This is a β lactam anti-microbial which is viable for treatment of bacterial contaminations like tonsillitis, pneumonia, bronchitis, gonorrhoea, ear contamination, urinary tract contamination, ulcers and skin disease.

These contaminations are fundamentally brought about by Helicobacter pylori which for the most part live in gastric mucosal layer. So the focus and occupant time of amoxicillin is significant for complete annihilation of H. Pylori (Risbud *et al.*, 2000). The ordinary conveyance framework for amoxicillin has short occupant time in stomach.

A decent method to improve the adequacy of treatment is to build up a medication conveyance framework which can live in the stomach for longer span and discharge tranquilize as long as conceivable in the natural specialty of the bacterium, and subsequently Gastro retentive Drug Delivery System (GRDDS) is an extreme answer for this (Sahasathian *et al.*, 2007; Bardonnet *et al.*, 2006).

The present investigation was planned for developing a sintered floating tablets of Antibacterial drug. Carnauba wax polymer with melting point 82^0-86°C, it was chosen as the polymer for sintering and was proposed to test its applicability in design of gastro retentive floating tablets.

MATERIALS AND METHODS

Reagents and Chemicals

Amoxicillin trihydrate was provided by yarrowChem (Mumbai, India). Carnuaba wax, sodium bicarbonate and magnesium stearate were obtained from yarrow Chem. products (Mumbai, India). All other reagents were of analytical grade.

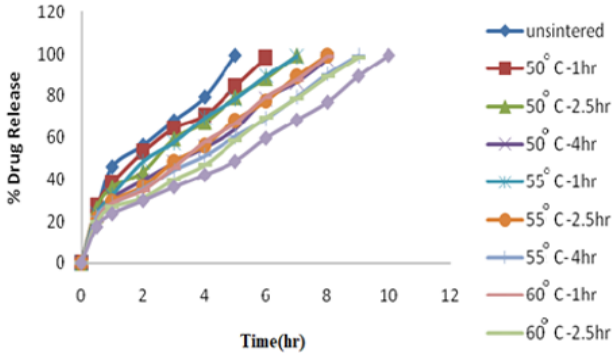

Figure 1: Dissolution profile of AC1

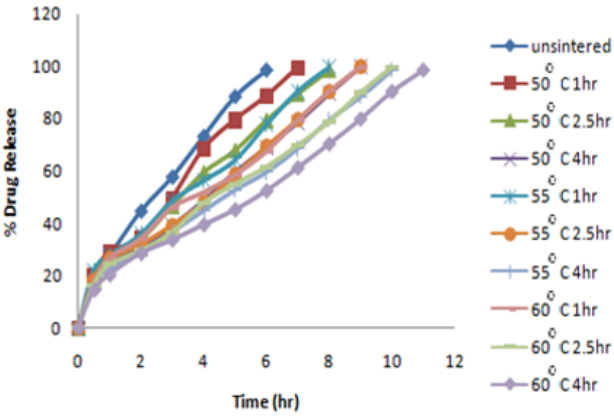

Figure 2: Dissolution profile of AC2

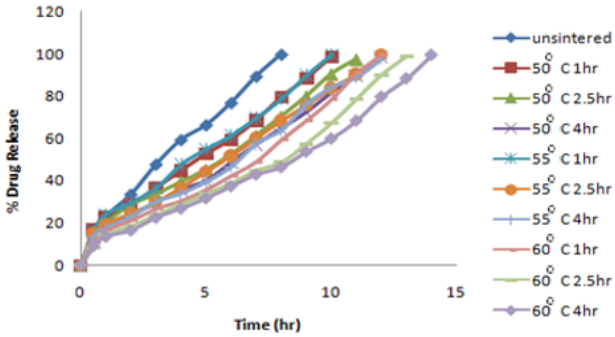

Figure 3: Dissolution profile of AC3

Preparation of GRFT

All the ingredients were accurately weighed according to the formulae mentioned in Table 1 screened to sieve # 40. Drug mixed with Carnauba Wax until homogeneous mixture was achieved. Sodium bicarbonate and Micro crystalline cellulose were added and mixed for 5 minutes in a polybag. To the above mixture solution of Isopropyl Alcohol with Povidone k30 was added to get coherent mass and sifted through # 10. Dried the granules for 15 min at 45^0C. Granules were sifted through sieve number # 22. The dried granules lubricated with pre-sifted magnesium stearate and talc. then mixed for 3 min

Table 1: Formulae of gastroretentive amoxicillin floating tablets

Ingredients	AC1	AC2	AC3
Amoxicillin	500	500	500
Carnauba wax	80(10%)	100(13%)	120(15%)
Sodium bicarbonate	40	40	40
HPMCK4M	40	40	40
MCC	92.5	82.5	72.5
Povidone k30	q.s	q.s	q.s
Magnesium stearate	7.5	7.5	7.5
IPA	QS	QS	Q.S
Total	760	770	780

Table 2: AC1 Tablet Characteristics and buoyancy characteristics

Sintering temp and time	Weight in (mg)	Assay in (%)	Hardness in (Kg/cm^2) AC1	Friability in (%)	Floating lag time in (sec)	Total floating time in (h)
unsintered	759.6±5.01	99.1±0.92	4-6	0.31	143±4	5
50^0C- 1 hr	758.5±3.23	100.8±0.41	4-6	0.42	131±6	6
50^0C- 2.5 hr	760.4±2.43	100.3±1.13	4-6	0.28	120±3	7
50^0C -4 hr	761.1±1.31	101.6±0.61	4-6	0.38	113±4	8
55^0C -1 hr	760.3±3.32	99.3±1.32	4-6	0.33	116±1	7
55^0C -2.5hr	761.3±4.12	99.3±1.45	4-6	0.41	86±3	8
55^0C -4hr	759.5±5.62	100.2±0.75	4-6	0.26	73±2	9
60^0C -1 hr	760.1±5.23	99.1±1.06	4-6	0.35	65±4	8
60^0C -2.5 hr	759.7±4.32	101.2±1.68	4-6	0.26	51±3	9
60^0C -4hr	760.1±3.74	99.8±1.53	4-6	0.38	40±4	10

Table 3: AC2 Tablet Characteristics and buoyancy characteristics

Sintering temp and time	Weight in (mg)	Assay in (%)	Hardness in (Kg/cm^2) AC2	Friability in (%)	Floating lag time in (sec)	Total floating time in (h)
unsintered	769.1±2.31	99.4±1.23	4-6	0.43	166±2	6
50^0C 1 hr	771.2±1.89	99.8±1.56	4-6	0.35	154±3	7
50^0C 2.5 hr	770.2±3.02	99.6±1.84	4-6	0.48	146±2	8
50^0C 4 hr	771.2±2.65	99.4±0.96	4-6	0.37	132±1	9
55^0C 1 hr	770.7±3.11	99.2±1.13	4-6	0.39	137±4	8
55^0C 2.5hr	771.3±2.87	99.3±1.08	4-6	0.33	114±2	9
55^0C 4hr	769.1±4.31	100.2±0.75	4-6	0.41	103±6	10
60^0C 1 hr	770.1±3.23	99.7±1.63	4-6	0.34	105±5	9
60^0C 2.5 hr	769.4±2.75	100.1±1.23	4-6	0.29	82±4	10
60^0C 4hr	770.7±2.13	99.8±1.64	4-6	0.48	73±2	11

Table 4: AC3 Tablet Characteristics and buoyancy characteristics

Sintering temp and time	Weight in (mg)	Assay in (%)	Hardness in (Kg/cm^2)	Friability in (%)	Floating lag time in (sec)	Total floating time in (h)
			AC3			
unsintered	779.5±3.41	99.5±1.87	4-6	0.33	176±3	8
50^{0}C 1 hr	781.7±2.12	100.8±0.42	4-6	0.36	163±1	10
50^{0}C 2.5 hr	780.5±4.12	99.6±1.01	4-6	0.48	156±2	11
50^{0}C 4 hr	781.4±2.43	99.9±1..23	4-6	0.41	132±4	12
55^{0}C 1 hr	780.1±3.67	99.4±2.43	4-6	0.31	137±1	10
55^{0}C 2.5hr	781.8±1.34	99.8±3.12	4-6	0.43	124±5	12
55^{0}C 4hr	779.2±2.31	100.1±0.65	4-6	0.21	113±3	12
60^{0}C 1 hr	780.1±3.26	99.9±1.04	4-6	0.34	115±4	12
60^{0}C 2.5 hr	779.4±1.78	100.1±0.64	4-6	0.39	106±2	13
60^{0}C 4hr	780.2±2.65	99.6±1.43	4-6	0.38	97±5	14

Table 5: AC1 Analysis of Drug release kinetics

Sintering temp and time	Zero order r	First order r	Higuchi model r	Peppas r	Peppas n
unsintered	0.9268	0.7253	0.9363	0.9680	0.537
50^{0}C -1 hr	0.9345	0.8026	0.9347	0.9925	0.493
50^{0}C- 2.5 hr	0.9508	0.7434	0.9127	0.9817	0.497
50^{0}C- 4 hr	0.9640	0.8181	0.8630	0.9667	0.501
55^{0}C -1hr	0.9551	0.8202	0.9422	0.9975	0.547
55^{0}C -2.5 hr	0.9753	0.7106	0.8758	0.9752	0.549
55^{0}C -4 hr	0.9738	0.7079	0.8480	0.9601	0.515
60^{0}C -1 hr	0.9789	0.7699	0.8748	0.9727	0.569
60^{0}C -2.5 hr	0.9814	0.7666	0.8313	0.9496	0.559
60^{0}C- 4 hr	0.9763	0.8834	0.8225	0.9556	0.546

Table 6: AC2 Analysis of Drug release kinetics

Sintering temp and time	Zero order r	First order r	Higuchi model r	Peppas r	Peppas n
unsintered	0.9833	0.8377	0.9244	0.9949	0.669
50^{0}C 1 hr	0.9784	0.7733	0.8828	0.9661	0.618
50^{0}C 2.5 hr	0.9820	0.8051	0.8908	0.9819	0.608
50^{0}C 4 hr	0.9849	0.6879	0.8411	0.9602	0.589
55^{0}C 1hr	0.9770	0.6984	0.8604	0.9666	0.552
55^{0}C 2.5 hr	0.9835	0.6822	0.8355	0.9585	0.577
55^{0}C 4 hr	0.9823	0.9152	0.8499	0.9689	0.569
60^{0}C 1 hr	0.9779	0.6475	0.8722	0.9830	0.583
60^{0}C 2.5 hr	0.9801	0.9103	0.8650	0.9745	0.573
60^{0}C 4 hr	0.9773	0.9378	0.8495	0.9757	0.567

Table 7: AC3 Analysis of Drug release kinetics

Sintering temp and time	Zero order r	First order r	Higuchi model r	Peppas r	Peppas n
unsintered	0.9870	0.6487	0.9127	0.9969	0.710
50^0C 1 hr	0.9823	0.9152	0.8499	0.9689	0.569
50^0C 2.5 hr	0.9773	0.9378	0.8495	0.9757	0.567
50^0C 4 hr	0.9811	0.9590	0.8383	0.9665	0.574
55^0C 1hr	0.9801	0.9103	0.8650	0.9745	0.573
55^0C 2.5 hr	0.9823	0.9578	0.8292	0.9515	0.559
55^0C 4 hr	0.9772	0.9236	0.8053	0.9525	0.577
60^0C 1 hr	0.9772	0.7584	0.8308	0.9678	0.605
60^0C 2.5 hr	0.9833	0.6727	0.8735	0.9848	0.628
60^0C 4 hr	0.9847	0.4453	0.8497	0.9740	0.593

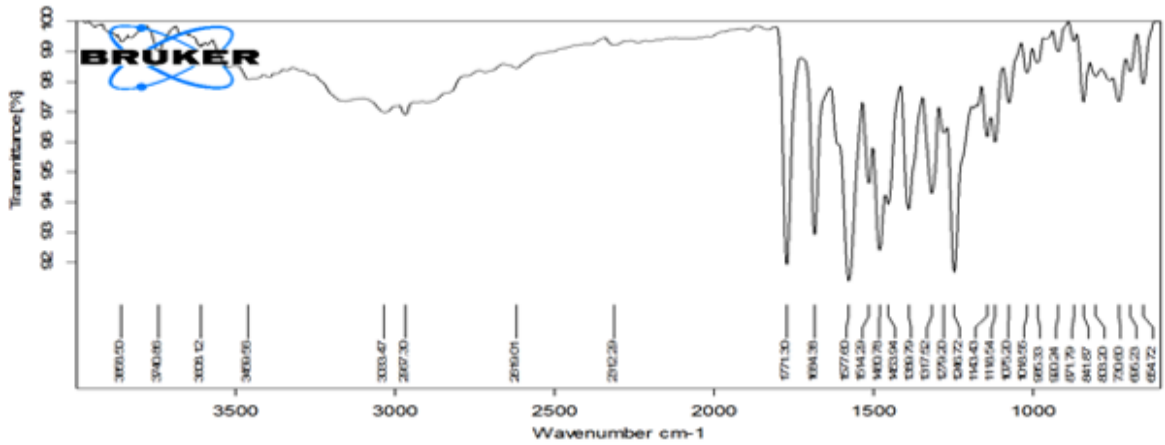

Figure 4: FTIR of pure drug

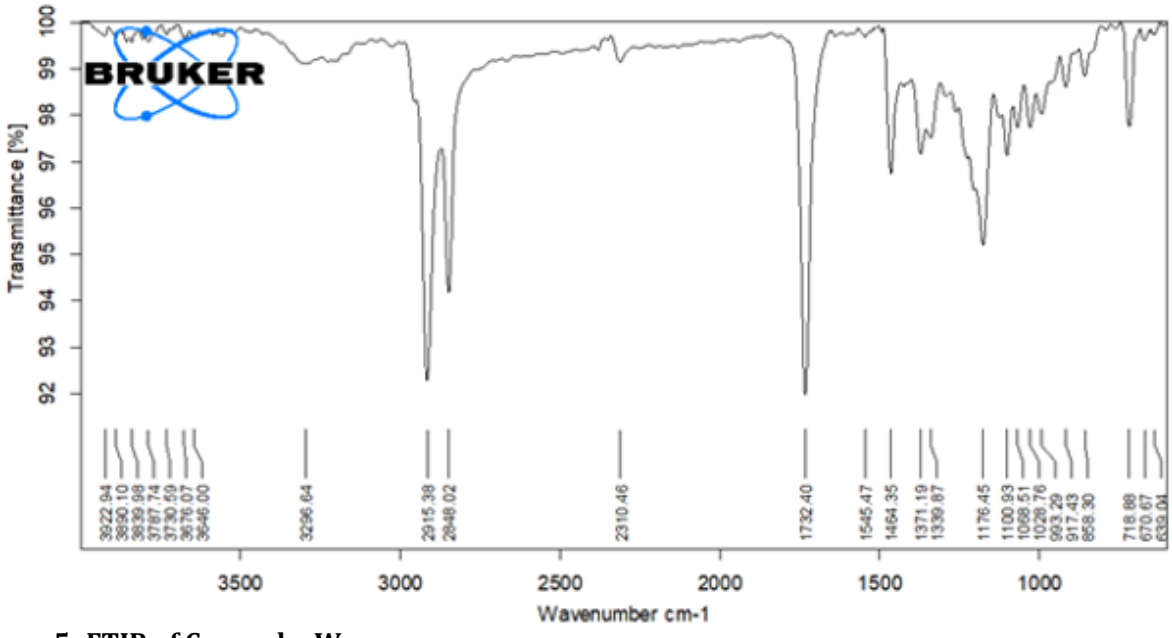

Figure 5: FTIR of Carnauba Wax

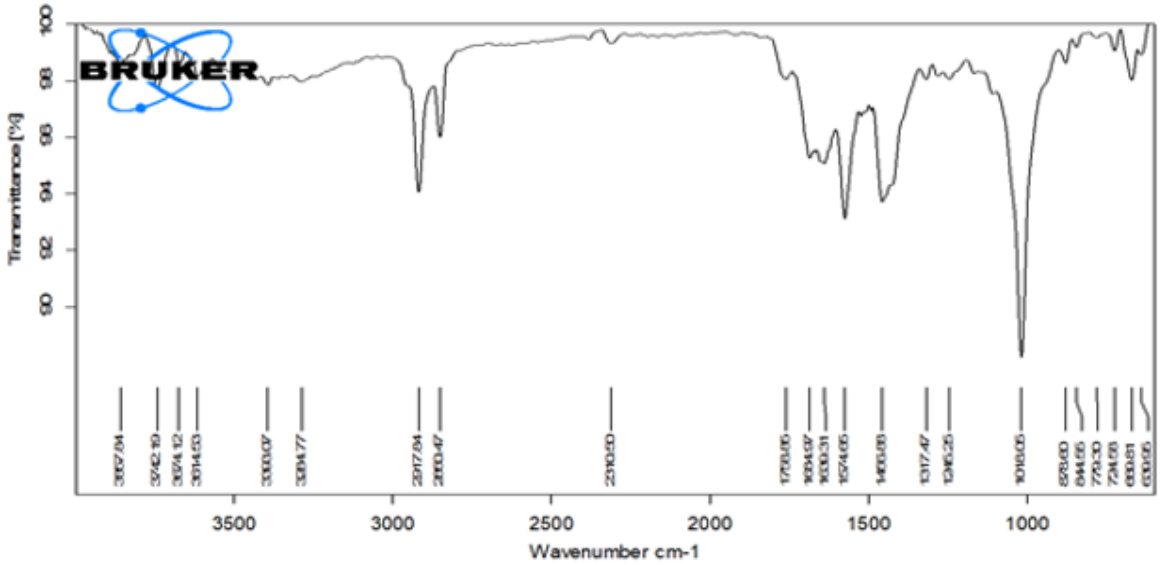

Figure 6: FTIR of Drug, polymer and thermally sintered optimized formulation

in a polybag. Blend was compressed into tablets using 12mm punches at the compression force of 4-6 Kg/cm^2.

Preparation of floating tablets with thermally sintering

Three specific temperatures were exposed to the tablets viz., 50°C, 55°C and 60°C and for three various time duration of 1h, 2.5h and 4 in a hot air oven. After sintering tablets were cooled to room temperature.

Invitro evaluation of floating tablets

In vitro buoyancy studies

The floating lag time and total floating time was done by placing tablet in 1 liter glass beaker containing 500 mL of 0.1N HCl (Srikanth *et al.*, 2011). Results are mentioned in Tables 2, 3 and 4.

In vitro dissolution

Invitro drug release from unsintered and sintered floating tablets were studied employing the paddle method (Apparatus- II). 0.1N HCl was used as a medium maintained at a temperature of 37±0.1°C with a rpm of 50. 5 mL samples were withdrawn and replaced with 5 mL of fresh medium immediately and samples were measured at 230 nm.

Kinetics of drug release

A kinetic study explains release Profile as function of a few parameters with the assist of mathematical parameters for clean interpretation of the values. These techniques seem to be helpful in The formula improvement level which Includes Zero order (Lazarus and Cooper, 1961), first order (Wagner, 1969), Higuchi (Higuchi, 1963) and Korsmeyer-Peppas (Peppas, 1985) models. The version with the very best correlation coefficient (r) become judged to be a greater appropriate version.

Fourier Transform Infrared Spectroscopy

Amoxycillin trihydrate, polymers and drug polymer mixture have been subjected to FTIR examine. Sample combined with dried potassium bromide and compressed to shape a KBr disk. Samples had been scanned from 4000 to 400 cm^{-1}.

RESULTS AND DISCUSSION

Un-sintered as well as thermally sintered tablets of Amoxicillin trihydrate prepared with Carnauba wax, complied with compendia popular for uniformity of weight. hardness of all tablets formulations was observed in vary of 4 to 6 kg/cm^2. Drug content was observed in the range of 99% to 101%. Friability test was located to be less than 0.5%. The floating lag times of all Unsintered and sintered tablets were ranged from 40 to 176 sec. If increase in sintering temperature, the floating lag time could be reduced because of decreased porosity.

During sintering, the gaps between particles may decrease and each particle will quickly be exposed to surface of gastric fluid, leading to decrease in duration of the floating lag. Total floating times of unsintered and sintered tablets were in the range of 5-14 hr. As sintering temperature increased, the overall floating time could be increased due to creation of strong welded bonds between particles," which would keep the tablet stable for longer period of time".Sintering time was inversely proportional to floating lag time and directly commensurate with total floating time.The Figures 1, 2 and 3 indicate the combined percentage of product released from

sintered and non-sintered formulations. The formulation of AC1 releases greater than 97% of drug in 6, 7 and 8h respectively when exposed to 50^0C for 1, 2.5 and 4h. Formulation AC1 delayed the drug for up to 7, 8 and 9h respectively, when exposed to 55^0c for 1, 2.5 and 4h. Formulation AC1 delayed the drug for up to 8, 9 and 10h respectively, when exposed to 60^0c for 1, 2.5 and 4h. The formulation of AC2 released above 98% of the drug in 7,8 and 9h respectively when exposed to 50^0C for 1, 2.5 and 4h. The formulation of AC2 released of the drug maintained up to 8, 9 and 10h respectively when exposed to 55^0C for 1, 2.5 and 4h. The formulation of AC2 released of the drug maintained up to 9, 10 and 11h respectively when exposed to 60^0C for 1, 2.5 and 4h.The formulation AC3 (without sintering) delayed the drug by only 8h and same batch tablets kept at 50^0 c for 1h, 2.5h and 4h respectively delayed the drug 10, 11 and 12h at 55^0c for 1,2.5 and 4h respectively delayed the drug by 10, 12 and 12h . Same batch at 60^0c for 1, 2.5 and 4h respectively delayed the drug by 12, 13 and 14h. From the outcomes, it changed into observed that because the attention of polymer increases, release of drug turned into delayed which can be because of multiplied intensity of air wallet surrounded jellified film covering tablet (Murhty *et al.*, 2003). As the temperature for sintering and the time of sintering process upgrades, drug release was decreased. The property of the retarding drug may be the result of welded bonds forming via softening the polymer, drug particles may have been caught in shaped matrix resulting in controlled release. Tables 5, 6 and 7 presents the results of curve fitting dissolution data to the specific kinetic models. All tablets adopted zero order kinetics and follows non-Fickian diffusion mechanism. Formulation AC3 shows 12 hrs delayed release was obtained at sintering temperature 50^0c for 4hrs was chosen as an optimized formulae from the in vitro dissolution data.

Fourier transformation infrared spectroscopy

FTIR spectrum of Amoxicillin Trihydrate, Carnauba Wax and Optimized Formulation were showed in Figures 4, 5 and 6. Amoxicillin Trihydrate showed characteristic water of crystallization , OH stretch shown at 3520 cm^{-1}, Amide NH indicates at 3458 cm^{-1},Phenol OH stretch at 3175 cm^{-1}, Benzene ring CH stretch at 3046 cm^{-1}, Methyl CH stretch at 2964 cm^{-1}, β- Lactam CO stretch at 1775 cm^{-1}, Amide I CO stretch at 1686, COO^- asymmetric stretch and NH_3^+ deformation at 1580 cm^{-1}, Benzene C=C stretch at 1517 cm^{-1}, Amide II, NH band CN stretch band , NH_3^+ symmetric at 1482 cm^{-1}, dimethyl CH deformation at 1396 cm^{-1} .phenol OH band at 1378 cm^{-1},COO^- stretch 1327 cm^{-1},Fused thiazolidine β-lactam at 1314 cm^{-1} , Amide III , NH bend CN in plane combination band at 1283 cm^{-1}, phenol CO combination band at 1250 $cm^{-1}$and benzene CH in plane deformation 1143,1120 cm^{-1} (Thombre and Gide, 2016). The FTIR of Carnauba wax showed characteristic features of esters: carbonyl (C=O) stretching at 1735 cm^{-1} . C-C(= O)-O stretching at 1166 cm^{-1}, Optimised formulation showed characteristics peaks of amoxicillin trihydrate. There is no sign of band shift and broadening compared to spectra of pure drug. The results indicated that there were no chemical interactions.

Based on observations in FTIR spectra for the selected formulation indicated the there was no chemical interaction between drug and polymer.

CONCLUSIONS

In order to decrease polymer concentration with desired dissolution profile, the concept of the thermal sintering was studied. Experimental data concluded that floating lag time have been reduced and total floating times have been increased with the duration of sintering temperature exposure. Therefore, the release of in vitro drug has been delayed by increasing the time of exposure to temperature. It can therefore be inferred that thermal sintering technique can be used as a retarding polymer in the design of GRFT.

REFERENCES

Bardonnet, P. L., Faivre, V., Pugh, W. J., Piffaretti, J. C., Falson, F. 2006. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. *Journal of Controlled Release*, 111(1-2):1–18.

Cohen, J., Siegel, R. A., Langerx, R. 1984. Sintering Technique for the Preparation of Polymer Matrices for the Controlled Release of Macromolecules. *Journal of Pharmaceutical Sciences*, 73(8):1034–1037.

German, R. M. 1996. Sintering theory and practice. New York: Wiley-Interscience;1 edition. page 569.

Higuchi, T. 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences*, 52(12):1145–1149.

Hornsby, P. R., Maxwell, A. S. 1992. Mechanism of sintering between polypropylene beads. *Journal of Materials Science*, 27(9):2525–2533.

Lazarus, J., Cooper, J. 1961. Absorption, Testing, and Clinical Evaluation of Oral Prolonged-Action Drugs. *Journal of Pharmaceutical Sciences*, 50(9):715–732.

Murhty, K. V. R., Seshasayana, A., Himasankar, K., Raju, Y. P. 2003. Design and evaluation of ethylene vinyl acetate sintered matrix tablets. *Indian Journal of Pharmaceutical Sciences*, 65(5):496–499.

Peppas, N. A. 1985. Analysis of Fickian and non-Fickian drug release from polymers. *Pharmaceutica Acta Helvetiae*, 60(4):110–111.

Risbud, M. V., Hardikar, A. A., Bhat, S. V., Bhonde, R. R. 2000. pH-sensitive freeze-dried chitosan–polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. *Journal of Controlled Release*, 68(1):23–30.

Sahasathian, T., Kerdcholpetch, T., Chanweroch, A., Praphairaksit, N., Suwonjandee, N., Muangsin, N. 2007. Sustained Release of Amoxicillin from Chitosan Tablets. *Archives of Pharmacal Research*, 30(4):526–531.

Singh, R., Poddar, S. S., Chivate, A. 2007. Sintering of wax for controlling release from pellets. *AAPS PharmSciTech*, 8(3):E175–E183.

Srikanth, M. V., Rao, S., Sunil, N., Sharma, S. A., Uhumwangho, G. S., U, M., murthy KV, R. 2011. Formulation and evaluation of Gastro retentive floating drug delivery system of ofloxacin. *Drug Invention Today*, 3(3):7–9.

Thombre, N. A., Gide, P. S. 2016. Floating-bioadhesive gastroretentive Caesalpinia pulcherrima- based beads of amoxicillin trihydrate for Helicobacter pylori eradication. *Drug Delivery*, 23(2):405–419.

Wagner, J. G. 1969. Interpretation of Percent Dissolved-Time Plots Derived from In Vitro Testing of Conventional Tablets and Capsules. *Journal of Pharmaceutical Sciences*, 58(10):1253–1257.