ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

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

Polysaccharide-Based Controlled Release Systems for Antipsychotic Therapeutics Delivery

Pranati Srivastava*[1], Pushpendra Kumar Tripathi[2]

[1]Amity Institute of Pharmacy, Amity University Lucknow Campus, Chinhat, Lucknow-226028, Uttar Pradesh, India
[2]Rameshwaram Institute of Technology and Management, Sitapur, Lucknow- 227202, Uttar Pradesh, India

Article History:

Received on: 28 Mar 2020
Revised on: 30 Apr 2020
Accepted on: 02 May 2020

Keywords:

Biopolymer,
Pectin,
Micro encapsulation,
Antipsychotic drug,
Drug release,
Drug delivery system

ABSTRACT

Researches in pharmaceutical fields are now focusing on biopolymer-based drug delivery systems for treatment of mild to severe diseases. Amongst all biopolymers, pectin is one of the frequently available and eco-friendly bio-polymer extracted from different fruit peels and abundantly available in nature. This study focuses to extract the pectin from two different fruits using different methods namely hot water-based extraction and cold maceration, involving two different fruit peels. Post extraction and isolation of polymer, study was performed for characterization of pectin powder by particle shape, particle size distribution, surface area angle of repose, flowability and tapped density. The obtained pectin was used for anti-psychotic drug delivery when incorporated into microspheres by solvent evaporation method. It's surface morphology and release kinetics was analyzed using *in vitro* methods and *in vivo* models and kinetics of drug release (goodness of fit) was assessed. The result revealed that the pectin extracted from mango peel using soxhlation method showed good flow rate, minimum particle size and shape distribution, porosity etc. Moreover, it showed the better drug release data in both *invitro* and *in-vivo* analysis. The study concludes that in future the natural biopolymer like pectin stands as a potential candidate for formulation of drug release system for efficient delivery of drug.

*Corresponding Author

Name: Pranati Srivastava
Phone: +91-8400154076
Email: psrivastava6@lko.amity.edu

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i3.2501

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

In the past decade, systematic drug delivery plays a key role in various clinical aspects. In this connection numerous nanomaterials have been used as vehicle for drug delivery, but it cruelly hampered owing to low efficacy of delivery to the target site and fast discharge from the body before instigating their action (Reis, 2019). Consequently, the researchers focused on bioinspired drug delivery system like biopolymers.

Polysaccharides like starch, pectin, cellulose are different natural polymers which have been used for delivering various types of drug doses. They are applicable in various fields like food industry, pharmaceutical industry and cosmetics sector (Shirwaikar *et al.*, 2008; Patil *et al.*, 2013).

Most of the natural polymers are built by the process of condensation followed by polymerization. The advantage of use of biopolymers are bio degradable in nature, nontoxic/ non - inflammatory, they

are also biocompatible as their rate of degradation is inversely proportional to chemical modification. Compare to synthetic polymer the natural polymer is highly porous, able to attached with other molecule as they have various functional groups (Kuo *et al.*, 2013; Baggi and Kilaru, 2016). Moreover, it is cost effective renewable sources.

Pectin is one of the most abundant, plant derived and naturally available biopolymer using in various fields like drug delivery, Nutraceuticals, tissue engineering, Pharmaceutics etc. (Masheer, 2013).

It is nontoxic, eco-friendly polymer used as gelling and emulsifying agent in food industries (Noreen *et al.*, 2017).

In drug delivery system the hydrophilic properties of pectin decrease the ability to control efficient drug release in target site (Rao *et al.*, 1995; Ando *et al.*, 2012; Ruoslahti *et al.*, 2010).

To overawed this disadvantage physical, chemical and enzymatic modifications of pectin is in practice. Recently the pectin unified with various compounds like cellulose, starch, chitosan, PEO, collage metal-oxides etc. and applying in wide areas.

This pectin composites with LDH are applied to control drug release in stomach and intestine for colonic disease and ulcerative crohn's disease (Guo *et al.*, 2010; Leroux *et al.*, 2012) Pectin collagen composites are used as bone substitute, salicylate-based composite has antimicrobial activity it is help to prepare for food packaging (Gorrasi and Bugatti, 2016).

Pectin CMC based composite are used for scaffold production in tissue engineering (Agoda-Tandjawa *et al.*, 2012). Pectin based powders and nanoparticles are applied in colon specific drug delivery medium and wound dressing (Wong *et al.*, 2011; Rossi *et al.*, 2010).

Apart from these, extra ordinarily the pectin is involved in brain targeting drug delivery system, numerous approaches were established to progress the brain specific drug delivery by engineering nanoparticles-based drug delivery systems. While remarkable growth has been made, but the drug delivery productivity is still remote (Gao, 2016).

The pectin based nasal inserts can improve bioavailability of antipsychotic drugs with chlorpromazine hydrochloride due to its mucoadhesion capacity (Luppi *et al.*, 2010) and low methylated pectin have been exposed to gel and be retained in the nasal cavity after deposition so it could expand the proficiency of the direct nose to brain pathway particularly for drugs for treatment of central nervous system disorders (Charlton *et al.*, 2007).

In the present study focus the antipsychotic drug release system using pectin derived from different fruits and applied with Chlorpromazine for the treatment of psychiatric disorders (Ranbhise and Kamat, 2014).

MATERIALS AND METHODS

The Mango and Orange peels were obtained from local market of Lucknow, Uttar Pradesh. The drug Chlorpromazine was procured from Salvavidas™ Pharmaceuticals private limited, Surat, Gujrat. Other excipients like Poly-Lacto Glycolic Acid, Dichloromethane and Ethanol were purchased from Sigma and Himedia. The synthetic pectin was procured from Sigma Aldrich. The fruit peels were subjected to different temperature and solvent conditions for cold soak (maceration) and hot water-based extraction.

Extraction and isolation of polymer using cold soak/ maceration

Fresh fruit peels were comminuted for easy solvent capturing. 100g of fruit peels were soaked individually in Acidified water and cyclohexane diamine tetra acetic acid (Trans- CDTA) (4% v/v) in 1:10 ratio with pH 2.0 (0.1N citric acid as pH modifier) for 30 days with occasional stirring. Throughout the experiment temperature was maintained at 20°C to 30°C. Then the pectin was precipitated using 95% ethyl alcohol and incubate for 6 hours at RT.

After incubation, the entire content was filtered using four-fold muslin cloth and the filtrate was treated with 95% ethyl alcohol again and centrifuged at 10000 rpm for 30 min. collect the pellet and washed with acetone of LR grade and dried in hot air oven below 40°C for 5-6 hrs. The Powder was obtained and passed through sieve number #80 and stored in refrigerator.

Extraction and isolation of polymer using hot water-based extraction

The process of Soxhlation was used for carried out the extraction process. 100g of dried peel powder was taken in round bottom flask with 1:8 ratio of acidified water (pH 2) and heated up to 75°C for 6h to 8h after first siphon cycle. During the procedure, the temperature was continuously monitored, and pH was sustained. After the soxhlation procedure, the ethyl alcohol was mixed in 2:1 to the flask and continuously stirred at 4°C for 2 hrs for precipitation. Precipitated pectin was filtered through four-fold muslin cloth and washed three times with iso-propyl alcohol. The precipitate was dried below 40°C in hot air oven, sieved through sieve size #20 and stored in refrigerator (Srivastava *et al.*, 2017).

Table 1: Formulation Coding Using Different Polymeric Systems

Formulation	Polymer
F1	Orange Peel Pectin (Soxhlation)
F2	Mango peel pectin (Soxhlation)
F3	Orange Peel Pectin (Cold Soak)
F4	Mango Peel Pectin (Cold Soak)

Table 2: Results of Polymer Characterization & Flow Property Study

	Orange Peel Pectin (Soxhlation)	Mango peel pectin (Soxhlation)	Orange Peel Pectin (Cold Soak)	Mango Peel Pectin (Cold Soak)
Bulk density (mg/ml)	0.753±0.01	0.805±0	0.73±0.02	0.788±0.01
Tapped density (mg/ml)	0.98±0	0.967±0.04	0.897±0.02	0.95±0
True density (mg/ml)	0.055	0.055	0.052	0.053
Bulkiness (ml/mg)	1.325	1.242	1.37	1.287
Carr's index (%)	23.13	16.67	18.53	19.44
Hausner's ratio (%)	1.3	1.2	1.23	1.22
Porosity	92.7	93.17	92.87	93.19
Angle of repose (°)	15.64	10.23	14.25	20.83
pH	6.6	6.8	6.8	6.7
Viscosity (Pascal)	34.16 ±0.03	36.22 ±0.10	40.20 ±0.02	43.13 ±0.34
% loss on drying	1.2 ± 0.06	2.0 ±0.11	1.18 ±0.05	2.31 ±0.08

The extracted pectin from fruit peels were characterized for various micromeritic properties, flow behavior, swelling properties etc. (Srivastava *et al.*, 2017).

The surface morphology of pectin was studied using Scanning Electron Microscopy (Sophisticated Analytical Instrumentation Facility (DST)" Department of Anatomy, All India Institute of Medical Sciences, New Delhi India).

Formulation of Microspheres Using Extracted Polymers

1gm of Pectin from various peels were separately dissolved in 400 ml of water followed by 1% Ammonium cerium (IV) sulphate dihydrate (0.005 M) was added and continuously stirred at RT for 2 hrs. Then Methylated PEG solution (1% w/v) was mixed. The reaction mixture was continuously stirred at RT for 48 hrs (Kim *et al.*, 2006; Kumbhar *et al.*, 2016; Vanitha and Desu, 2019).

Next to that 4% of PEG 6000 (dissolved in ethanol) was added into this complexed solution finally the 100mg of Chlorpromazine (dissolved in ethanol) was also added in a streamlined flow under continuous stirring.

The above solution was then added in a thin stream to a beaker containing a mixture of light liquid paraffin (90 ml), *n*-heptane (10 mL) and Polysorbate 80 (2 % *V/V*) in liquid paraffin and continuously stirred at 1000 rpm using mechanical stirrer at RT until the ethanol was evaporated completely for microsphere preparation.

The formed microspheres were filtered through Whatman no. 1 filter paper and washed 4–5 times with petroleum ether allowed to dried at RT for 24 hrs (Patil *et al.*, 2013).

The obtained microparticles were characterized by observing through optical microscopy, particle size and distribution, product yield, encapsulation efficiency and loading efficiency, micromeritic properties of particles, scanning electron microscopy and *invitro* release characteristics (Jelvehgari *et al.*, 2011). Table 1

For the drug entrapment study the microparticles equivalent to 10 mg Chlorpromazine were as dissolved in 10 ml 0.1 N HCl. This solution was then filtered through Whatmann filter paper No. 44. After suitable dilution (1μg/ml to 10 μg/ml dilution range), the absorbance was measured at 250 nm using UV spectrophotometer and the percentage drug entrapped was calculated. The drug entrapment study was conducted in triplicate (Dias-Souza *et al.*, 2017). The percentage of encapsulation was calculated (% Entrapment efficiency = Drug loading /Theoretical drug loading x 100) (Neha *et al.*, 2012).

Angles of repose of different formulations were calculated according to the fixed funnel standing method. Bulk density and tapped density were measured in a 10-mL graduated cylinder using a bulk density apparatus. Carr's compressibility index of microspheres was computed (8).

The SEM analysis was carried out by using Quanta 200 FEI, EDAX (Bettella *et al.*, 2017; Chandy *et al.*, 2009).

Drug Release Study

The *invitro* release of microparticles were taken in SGF (Simulated Gastric Fluid) of pH 1.2 prepared using 0.1 N HCl in 600 ml of fluid. The first two hour of release was taken in SGF.

Further release data was collected in phosphate buffer of pH 6.8 for one hour, followed by release study in PBS of pH 7.4 for 9 hours. 5ml aliqoutes were collected at predetermined interval and subsequently were replaced by 5ml of fresh buffer. The samples were analyzed by UV Spec. at 250 nm. The drug release was calculated and kinetic profile was determined.

The kinetic models like Zero-order equation, First-order equation, Higuchi kinetics and Korsemeyer-Peppas models were applied to all the formulations, suitable model was studied using regression coefficient (Schneider *et al.*, 2010).

The *in-vivo* analysis of drug release from microparticles were tested using Pole Climb Avoidance Test, which is a behavioral model for studying effect of antipsychotics on rats. The analysis with Cooks Pole Climbing Apparatus in Male Wistar rats (6 in each group).

The dose calculated was 10mg/kg bodyweight of the rats and the end point analysis sated the fact that neuroleptics enhance the time taken to climb the pole (expressed as latency) in Electric shocks through grid floor (Radahmadi *et al.*, 2013).

The latency in seconds were plotted for all the four formulations and was analyzed using a Kruskal-Wallis nonparametric one-way analysis of variance corrected for formulations and ties.

All data were reported as the mean $\pm$ standard error in spite of the probable no normality of the distribution of scores, because it seems these parameters provide a clearer indication. The *P* value less than 0.05 ($P < 0.05$) was considered as significant.

RESULTS AND DISCUSSION

The properties of pectin power were studied based on density and porosity and powder flowability these are important pharmaceutical properties that can be derived from particle shape, particle size distribution, surface area angle of repose, flow through an orifice, and tapped density.

These are the Traditional tests through a long history of extensive use, and reference in USP/EP guidelines (Ramankannan *et al.*, 2013).

In this study the obtained pectin powders from various methods Polymer Characterization & Flow Property Study was mentioned in Table 1 & Table 2.

One of the challenges of increasing the flowability by using flow additives in pharmaceutical aspects. (Rao and Sahoo, 2017; Sahoo *et al.*, 2017) Various parameters such as angle of repose, Carr's index, Hausner ratio are used to express flowability of powders (Hadjittofis *et al.*, 2017).

A good flow is indicated by a Hausner ratio greater than 1.25, and a poor flow may have a value of 1.5 (Clayton, 2019).

Nearly all the pectin powders showed same ratio from 1.2 to 1.3 so compare to others the mango peel pectin prepared from soxhalation method (F2) showed fair flow rate compare to others.

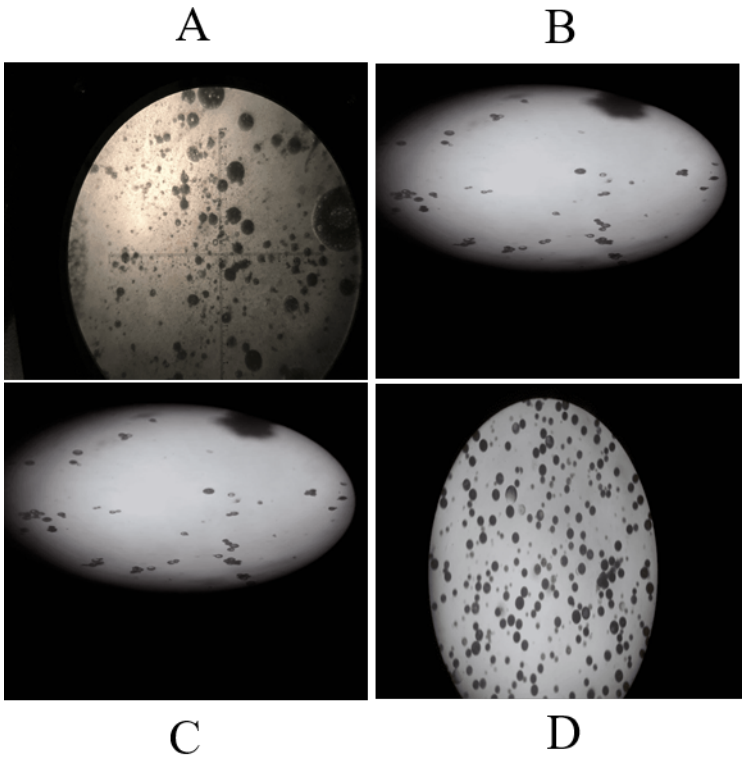


Figure 1: Optical Microscopy images of Microspheres of four formulations

Table 3: Observations of Various Formulations

Formulation code	Mean Particle Size (μm)	Shape	Shape uniformity	% Encapsulation Efficiency	% yield
F1	295±2.26	Spherical	Less	72.7±2.67	81.73±0.23
F2	332±3.15	Spherical	More	64.9±1.67	71.66±0.87
F3	374±3.72	Spherical	Less	28.2±0.57	25.82±1.45
F4	469±2.30	Spherical	Less	17.8±1.23	33.11±1.56

(± denotes the standard deviation among three sample readings taken);(*n=3)

Table 4: Summary of Release kinetics

Formulation	Polymer	Release kinetics followed
F1	Extracted Orange Peel Pectin (PoH)	Higuchi Kinetics
F2	Extracted Mango peel pectin (PmH)	Zero Order Kinetics
F3	Extracted Orange Peel Pectin (PoC)	Zero Order & Higuchi Kinetics
F4	Extracted Mango Peel Pectin (PmC)	First Order Kinetics

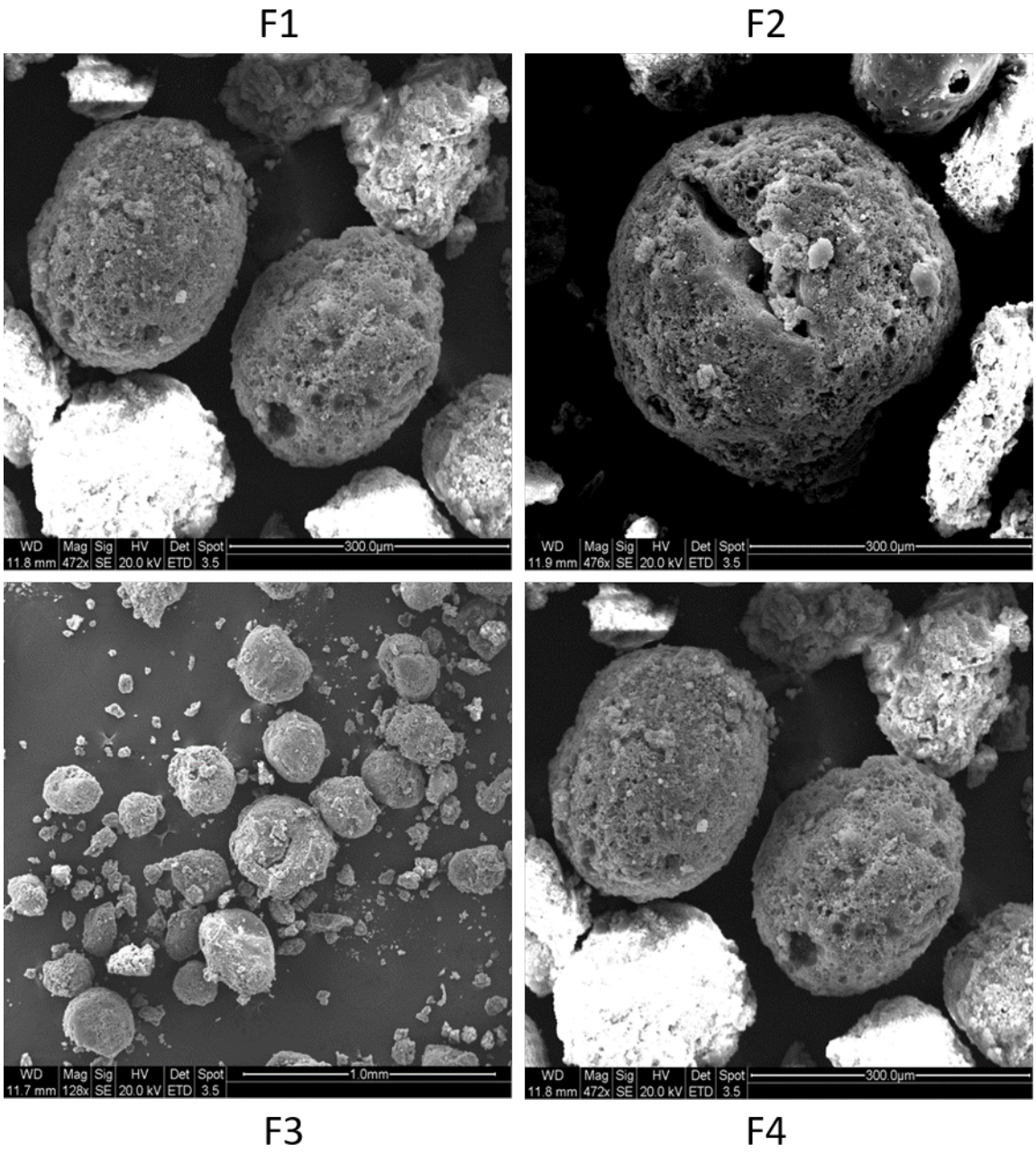


Figure 2: Morphological study of Microspheres using SEM

Carr's index calculation 5 – 21% is good flow rate (Patil *et al.*, 2018) all the powders are showed less than 20% except F1 and the Angle of repose < 30° is mentioned as good flow rate, here all the powders showed less than 21° So based on this equations all the four (F1-F4) powders showed good flowability but compared to other commercial pectin the pectin prepared from Mango peel (Soxhlation) F2 showed excellent flowability.

Study of particle shape, particle size distribution using microscopic analysis showed in Figure 1 & Figure 2 and Table 3.

The SEM micrographs in Figure 2 revealed that the resulting formulation were in a range of spherical to less spherical in nature with rough surfaces containing cracks and holes over its surface.

The reason behind this morphology change can be attributed to the faster evaporation of ethanol forming a pore like structure. From various SEM photographs, the size, mean diameter and its distribution of the microsphere the size of the prepared microspheres was uniform and appropriate for the study, but the shape uniformity more in F2 pectin compare to others.

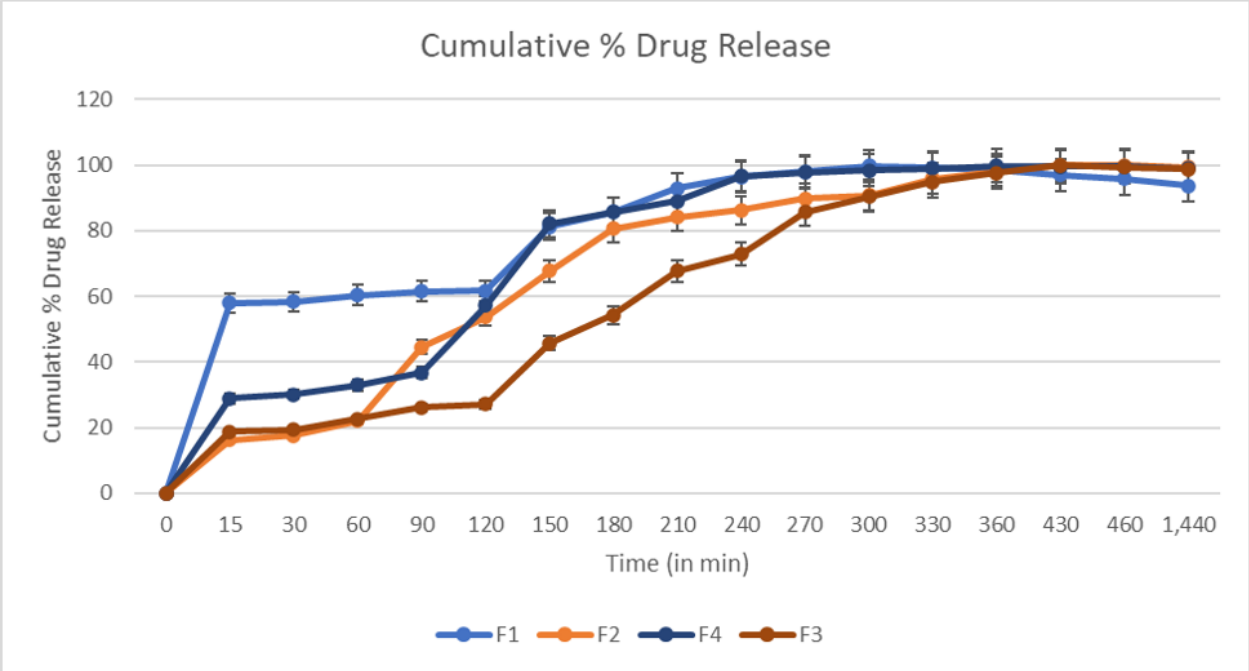
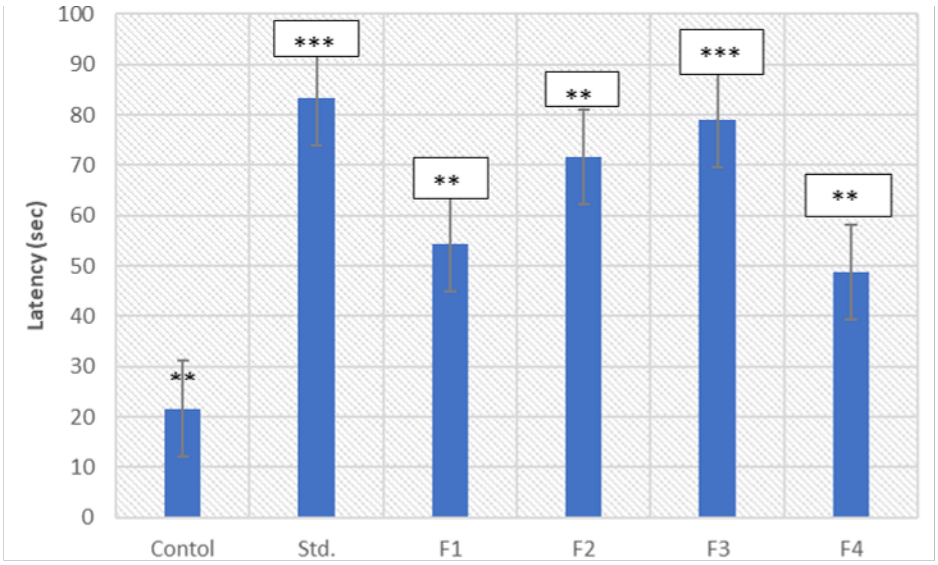


Figure 3: Invitrodrug release profile through different formulations (n=3)



** P<0.05, ***P<0.001 on the statistical analysis using one-way ANOVA and t-test

Figure 4: In-vivo Behavioral Study of drug treated Male Wistar rats

The mean particle size of the microsphere showed significant increase with the increase in polymer concentration and Particle sizes of the microspheres were found to be mainly affected by the concentration of polymer and stirring time used in the formulations.

The size ranges vary from 295 μm to 469 μm, smaller in size and shape uniformity of particle is better for various application in this connection the F1 and F2 pectin are exhibited smaller in size.

The percentage encapsulation efficiency of microparticles varied from 17.8% to 72.7%. The percentage loading of drug was increased by increasing the ratio of polymer as found high in all the formulation.

Encapsulation efficiency is the amount of drug entrapped within a colloidal system after a formulation process (Wake and Kshirsagar, 2017).

Better drug loading was achieved by increasing the ratio of polymer.

The percentage yield for all the microparticles was found in the range as 25-81%.

All the characteristic study result revealed that the F2 and some what the F1 pectin is better can applicable for various drug delivery systems.

In the *invitro* release pattern the obtained pectin entrapped drug is compared with comm0ercial pectin entrapped drug and released kinetics was studied (Figure 3 & Table 4).

According to the release pattern, it was observed that commercially obtained pectin released around 99% of drug at a time span of 330 minutes. The release could not be extended over 5 hours 30 minutes in comparison to 460 minutes release obtained from extracted pectin F2 Figure 3.

This can be attributed to the reason that acid-based extraction of pectin involves acids, which are the strongest extracting agents as they facilitate extraction of insoluble pectin that is tightly bound to the cell matrix of the plant material and result in higher yields.

On the other hand, commercially available pectin is obtained by either enzymatic extraction correlating with quicker and higher yield.

The *In-vivo* release pattern in rat model, compare to control all commercial and obtained pectin showed highest latency time. The latency time was had significantly high in F2 and F3 compare to control ($P < 0.001$) and F1 and F4 is also significantly increased ($P < 0.05$) Figure 4.

Finally, this study concludes that the natural pectin microencapsulation is used for good drug release in delivery system for psychiatric treatment.

CONCLUSION

The above studies identifies the fact that waste of fruits that is peels of Orange & Mango serve as potential candidate for pectin collection. More so ever, the pectin extracted by cold maceration technique is competitive enough to hot water based extraction in the view point that loss due to temperature rise and denaturation due to temperature rise do not occur. The study is supported by *invito* as well as *invivo* release data which envisage the path to cold maceration as prominent technique for extraction. Formulation of even surfaced microspheres by solvent evaporation method rules the fact that pectin is potential candidate to encapture the drug in efficient way and deliver at the required site as desired.

ACKNOWLEDGEMENT

The researcher is thankful to Rameshwaram Institute of Engineering & Technology for providing platform for research.

Conflict of Interest

Nil

Funding Support

Nil

REFERENCES

Agoda-Tandjawa, G., Durand, S., Gaillard, C., Garnier, C., Doublier, J. L. 2012. Properties of cellulose/pectins composites: Implication for structural and mechanical properties of cell wall. *Carbohydrate Polymers*, 90(2):1081–1091.

Ando, N., Kato, H., Igaki, H., Shinoda, M., Ozawa, S., Shimizu, H., Ikeda, K 2012. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Annals of surgical oncology*, 19(1):68–74.

Baggi, R. B., Kilaru, N. B. 2016. Calculation of predominant drug release mechanism using Peppas-Sahlin model, Part-I (substitution method): A linear regression approach. *Asian Journal of Pharmacy and Technology*, 6(4):223–223.

Bettella, G., Pozza, G., Kroesen, S., Zamboni, R., Baggio, E., Montevecchi, C., Zaltron, A., Gauthier-Manuel, L., Mistura, G., Furlan, C., Chauvet, M., Denz, C., Sada, C. 2017. Lithium Niobate Micromachining for the Fabrication of Microfluidic Droplet Generators.

Chandy, A., Rai, S., Manigauha, S., Sahu 2009. Entric-Coated Pectin Microspheres of Indomethacin for Targeting Inflammation in Lower Gastro intestinal tract. *Research J. Pharma. Dosage Forms and Tech*, 1(1):29–32.

Charlton, S. T., Davis, S. S., Illum, L. 2007. Evaluation of bioadhesive polymers as delivery systems for nose to brain delivery: In vitro characterisation studies. *Journal of Controlled Release*, 118(2):225–234.

Clayton, J. 2019. An Introduction to Powder Characterization. *Handbook of Pharmaceutical Wet Granulation*, pages 569–613.

Dias-Souza, M. V., Soares, D. L., Santos, V. L. 2017. Comparative study of free and liposome-entrapped chloramphenicol against biofilms of potentially pathogenic bacteria isolated from cooling towers. *Saudi Pharmaceutical Journal*, 25(7):999–1004.

Gao, H. 2016. Progress and perspectives on targeting nanoparticles for brain drug delivery. *Acta Pharmaceutica Sinica B*, 6(4):268–286.

Gorrasi, G., Bugatti, V. 2016. Edible bio-nano-hybrid coatings for food protection based on pectins and LDH-salicylate: Preparation and analysis of physical properties.

Guo, X., Zhang, F., Evans, D. G., Duan, X. 2010. Layered double hydroxide films: synthesis, properties and applications. *Chemical Communications*, 46(29):5197–5210.

Hadjittofis, E., Das, S. C., Zhang, G. G. Z., Heng, J. Y. Y. 2017. Interfacial phenomena. In Developing solid oral dosage forms.

Jelvehgari, M., Barar, J., Nokhodchi, A., Shadrou, S., Valizadeh, H. 2011. Effects of process variables on micromeritic properties and drug release of non-degradable microparticles. *Advanced pharmaceutical bulletin*, 1(1):18–18.

Kim, H. K., Chung, H. J., Park, T. G. 2006. Biodegradable polymeric microspheres with "open/closed" pores for sustained release of human growth hormone. *Journal of Controlled Release*, 112(2):167–174.

Kumbhar, D. M., Mali, K. K., Dias, R. J., Havaldar, V. D., Ghorpade, V. S., Salunkhe, N. H. 2016. Formulation and Development of Ethyl cellulose coated Pectin based Capecitabine Loaded Microspheres for Colorectal Cancer. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 8(4):261–261.

Kuo, C. K., Li, W. J., Tuan, R. S. 2013. Cartilage and ligament tissue engineering: biomaterials, cellular interactions, and regenerative strategies. *Biomaterials Science*, pages 1214–1236.

Leroux, F., Stimpfling, T., Hintze-Bruening, H. 2012. Relevance and Performance of LDH Platelets in Coatings. *Recent Patents on Nanotechnology*, 6(3):238–248.

Luppi, B., Bigucci, F., Abruzzo, A., Corace, G., Cerchiara, T., Zecchi, V. 2010. Freeze-dried chitosan/pectin nasal inserts for antipsychotic drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 75(3):381–387.

Masheer, A. K. 2013. Effect of Swelling and Drug Release Relationship of Sustained Release Matrices containing different Grades of Hydroxypropyl Methylcellulose. *Research J. Pharma. Dosage Forms and Tech*, 5(4):232–236.

Neha, A., Himanshi, K., Deepa, P., Nageen, A., Tarun, G. 2012. Evaluation of entrapment efficiency of glipizide microsphere. *IOSR J Pharm*, 2:180–181.

Noreen, A., i Huma Nazli, Z., Akram, J., Rasul, I., Mansha, A., Yaqoob, N., Iqbal, R., Tabasum, S., Zuber, M., Zia, K. M. 2017. Pectins functionalized biomaterials; a new viable approach for biomedical applications: A review. *International Journal of Biological Macromolecules*, 101:254–272.

Patil, D. M., Farooque, A. S., Bairagi, V. A. 2018. Formulation, Development And Evaluation of Sustained Release Matrix Tablet Of Methimazole. *Indo American Journal of Pharmaceutical Sciences*, 5(1):209–225.

Patil, S. R., Saudagar, R. B., Gondkar, S. B., Darekar, A. B. 2013. Formulation & evaluation of sustained release microspheres of Ropinirole hydrochloride. *Indian Journal of pharmacy professional and learners*, 1(1):11–012.

Radahmadi, M., Alaei, H., Sharifi, M. R., Hosseini, N. 2013. The effect of synchronized running activity with chronic stress on passive avoidance learning and body weight in rats. *International journal of preventive medicine*, 4(4):430–430.

Ramankannan, J., Gnana, R., Suganthi, N., Balaji, M., Seenuvasan 2013. Preparation and Characterization of Pectinase bound Co-precipitated Magnetic Nanoparticles. *Asian J. Pharm. Tech*, 3:175–180.

Ranbhise, S. S., Kamat, A. M. 2014. A Study to Assess the Knowledge Regarding Adverse Effects of Selected Antipsychotic Drugs among the Caregivers of Patients Receiving Antipsychotic Drugs. *Int. J. Nur. Edu. and Research*, 2(4):313–318.

Rao, S. R. M., Sahoo, C. K. 2017. Controlled Porosity Osmotic Pump Tablets of Zidovudine and Lamivudine Combination: Optimization and Characterization. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 9(3):114–114.

Rao, V. S. N., Silva, J. C. R., Medeiros, F. C. 1995. Effects of antiinflammatory plant extracts on ovoimplantation in rats. *Phytotherapy Research*, 9(6):458–459.

Reis, R. L. 2019. Encyclopedia of Tissue Engineering and Regenerative Medicine.

Rossi, S., Marciello, M., Bonferoni, M. C., Ferrari, F., Sandri, G., Dacarro, C., Grisoli, P., Caramella, C. 2010. Thermally sensitive gels based on chitosan derivatives for the treatment of oral mucositis. *European Journal of Pharmaceutics and Biopharmaceutics*, 74(2):248–254.

Ruoslahti, E., Bhatia, S. N., Sailor, M. J. 2010. Targeting of drugs and nanoparticles to tumors. *The Journal of Cell Biology*, 188(6):759–768.

Sahoo, K. C. K., Satyanarayana, D., Ramana, V. 2017. Kanhu Charan Panda. Formulation and Evaluation of Controlled Release tablets of Aspirin. *Asian J. Pharm. Tech*, 7(4):229–233.

Schneider, A., Hommel, G., Blettner, M. 2010. Linear regression analysis: part 14 of a series on evaluation of scientific publications. *Deutsches Ärzteblatt*

International, 107(44):776–776.

Shirwaikar, A., Shirwaikar, A., Prabhu, S., Kumar, G. 2008. Herbal excipients in novel drug delivery systems. *Indian Journal of Pharmaceutical Sciences*, 70(4):415–415.

Srivastava, P., Singh, M., Bhargava, S. 2017. A comprehensive study on fast dispersible and slow-releasing characteristic of orange peel pectin in relation to established synthetic polymer. *Pharmacognosy Magazine*, 13(51):401–401.

Vanitha, K., Desu, P. K. 2019. Formulation Development and Evaluation of Sodium Valproate and Valproic acid Extended Release Tablets. *Research Journal of Pharmaceutical Dosage Forms and Technology*, 11(2):74–74.

Wake, P. S., Kshirsagar, M. D. 2017. Compatibility study In-vitro drug release Study of Solid Lipid Nanoparticle Based Transdermal Drug Delivery System for Rasagiline Mesylate. *Asian Journal of Research in Pharmaceutical Science*, 7(2):92–92.

Wong, T. W., Colombo, G., Sonvico, F. 2011. Pectin Matrix as Oral Drug Delivery Vehicle for Colon Cancer Treatment. *AAPS PharmSciTech*, 12(1):201–214.