Preparation and characterization of mucoadhesive microcapsules of paclitaxel

Chinmaya Mahapatra¹, Padala Narasimha Murthy², Sudhir Kumar Sahoo², Anjan Kumar Mahapatra², Prasanna Kumar Dixit¹

¹Department of Zoology, Berhampur University, Bhanja Bihar, Odisha, India
²Royal College of Pharmacy and Health Sciences, Berhampur, Odisha, India

ABSTRACT

The objective of the present work is to develop paclitaxel encapsulated muco-adhesive microcapsules. The improvement aims to enhance its usefulness and control the drug release in cancer patients. Paclitaxel microcapsules with a coat consisting of sodium alginate and a muco-adhesive polymer such as acacia, Carbomer 941, Povidone K-30, Macrogol (PEG 6000) were prepared by ionotropic gelation technique. These microcapsules were evaluated for morphological characters, drug content, loading efficiency, drug-polymer interactions, swelling ratio, muco-adhesive properties and in vitro drug release. The resulting microcapsules were discrete, spherical, and free-flowing with a particle size range of 534 to 822 μm. The microencapsulation efficiency was 45.09–99.83%. The microcapsules prepared with alginate along with macrogol (F4M) have exhibited excellent muco-adhesive property in the in vitro wash-off test. The swelling ratio of microcapsules was enhanced with an increased alginate concentration, and the formulation (F4) showed the highest index of swelling, that is 2666. Paclitaxel release from these muco-adhesive microcapsules was slow and extended throughout six h and further depends upon the concentration of the alginate. The per cent drug release of alginate-acacia microcapsules (F4Ac) was higher than other formulations in the present study. In conclusion, alginate-acacia muco-adhesive microcapsules could be a promising vehicle for oral controlled release of paclitaxel.
tion approach of paclitaxel into an oral dosage form. As paclitaxel is a high molecular weight compound, its bioavailability can be enhanced by reducing its size to micro or nano range (Haggar and Boushey, 2009). The incidence of colorectal cancer in India is lower than that in western countries, and it is the seventh leading cancer in India (Gu et al., 2016). As per Globocan database in the year 2018, around 27,500 new cases of colorectal cancer have been found in India with about 19,500 death cases, and a total number of patients living with the disease was around 53,700 (Bray et al., 2018).

MATERIALS AND METHODS

Paclitaxel was obtained as a gift sample from Neon Laboratories Pvt. Ltd. and Naprod Life Science Pvt. Ltd., Boisor, India. Polymers such as acacia, carbomer 941, povidone K-30 and macrogol (PEG 6000) were obtained as gift samples from IPCA Laboratories Ltd., Athal, India. Sodium alginate, Eudragit S-100 and calcium chloride were procured from Thomas Baker, Merck and Loba Chemie Pvt. Ltd. All other chemicals used were of analytical grade.

Preparation of microcapsules

Microcapsules were prepared by using sodium alginate in combination with four muco-adhesive polymers, namely acacia, carbomer 941, povidone K-30, macrogol (PEG 6000) as coat materials. An orifice ionic gelation process has been used to prepare large-sized alginate beads (Surapaneni et al., 2012; Sarkar and Ahmed, 2016).

Microcapsules of paclitaxel with sodium alginate in a (drug: sodium alginate) ratio of 1:1, 1:2, 1:3 and 1:4 and with co-polymer (drug: sodium alginate: co-polymer) in a ratio of 1:2:2 were prepared by ionotropic gelation process. The drug was dissolved in methanol followed by purified water to make 2 mL of drug solution in methanol. Sodium alginate and co-polymers were dispersed in distilled water according to the formula given in Table 1 by using a stirrer. The drug solution was added into the polymer dispersion with continuous stirring. Then the drug-polymer dispersion was added dropwise at the rate of 1 mL/ m into 100 mL of CaCl\(_2\) solution (10% w/v) through a syringe with needle number-24 (0.55X 25 mm).

Further, the medium was stirred for 20 m at 200 rpm to complete the curing reaction and to produce spherical, rigid microcapsules. The microcapsules were collected by decantation, and the product thus separated was washed repeatedly with water, dried at 40 °C for 12 h and stored in a desiccator. The microcapsule compositions are listed in Table 1.

Evaluation of microcapsules

The prepared microcapsules were evaluated for particle size analysis, drug content, loading efficiency, swelling ratio, muco-adhesive properties, in-vitro release, morphological characters and drug-polymer interactions (Al-najjar and Hussain, 2017).

Size Analysis

The micro-particles were analyzed for particle size by using optical microscopy method. The instrument was calibrated, and a size of 100 micro-particles was calculated under magnification.

Per cent drug content

About 100 mg of prepared microcapsules were pow-
Table 1: Formulae of different microcapsules of paclitaxel

| Formula code | Drug: SA | Drug: SA:CO | Quantity (mg) | CaCl₂ % (w/v) |
|--------------|----------|-------------|---------------|---------------|
| F1           | 1:1      | –           | 50+50+0       | 10            |
| F2           | 1:2      | –           | 33.3+66.6+0   | 10            |
| F3           | 1:3      | –           | 25+75+0       | 10            |
| F4           | 1:4      | –           | 20+80+0       | 10            |
| F4Ac         | –        | 1:2:2       | 20+40+40      | 10            |
| F4C          | –        | 1:2:2       | 20+40+40      | 10            |
| F4M          | –        | 1:2:2       | 20+40+40      | 10            |
| F4P          | –        | 1:2:2       | 20+40+40      | 10            |
| F4F          | 1:4      | –           | 20+80         | 20            |
| F4G          | 1:4      | –           | 20+80         | 30            |
| F4J          | 1:4      | –           | 20+80         | 10            |
| F4K          | 1:4      | –           | 20+80         | 10            |

A-Alginate, Ac-Acacia, C-Carbomer, M-Macrogol, P-Povidone. F, G-Calcium chloride 20, 30, %wt/vol. J, K - Reaction time 10, 30 min, SA-sodium alginate, CO-Co-polymer.

Table 2: Drug content and encapsulation efficiency of different alginate microcapsules of Paclitaxel and commercial capsule

| Formulation code | Particle size (μm) | Drug content - (mg) | Microencapsulation efficiency (%) | Swelling index | t 50% (h) | % Drug released in 6 h (6 SD, n = 3) |
|------------------|-------------------|---------------------|----------------------------------|----------------|----------|-----------------------------------|
| F1               | 534 ± 1.2825      | 14.4                | 57.6                             | 1167           | 1.3      | 84.73                             |
| F2               | 578 ± 2.3416.6    | 10.7                | 64.5                             | 1428           | 1.4      | 82.46                             |
| F3               | 596 ± 1.7612.5    | 10.9                | 87.2                             | 1635           | 1.65     | 76.88                             |
| F4               | 624 ± 1.7810      | 9.23                | 92.3                             | 1876           | 1.8      | 64.23                             |
| F4Ac             | 746 ± 1.2410      | 9.82                | 98.2                             | 1278           | 1.5      | 99.5                              |
| F4C              | 822 ± 1.5210      | 4.59                | 45.9                             | 2666           | 1.7      | 69.65                             |
| F4M              | 672 ± 1.6410      | 9.47                | 94.7                             | 1438           | 1.8      | 85.44                             |
| F4P              | 783 ± 2.0810      | 9.65                | 96.5                             | 1210           | 1.65     | 97.23                             |
| F4F              | 628 ± 1.8210      | 9.41                | 94.1                             | -              | 1.85     | 62.46                             |
| F4G              | 612 ± 2.1310      | 9.44                | 94.4                             | -              | 2.2      | 61.13                             |
| F4J              | 631 ± 1.9410      | 9.08                | 90.8                             | -              | 1.68     | 68.62                             |
| F4K              | 620 ± 1.3610      | 9.14                | 91.4                             | -              | 2.25     | 65.40                             |

Results obtained are presented as an average of 3 determinations.

Accurately weighed micro-particles containing 25 mg of the drug were transferred to a beaker containing 100 mL in 0.5% w/v Sodium Lauryl Sulfate in distilled water. The mixture was allowed to stand for 24 hours. The amount of drug-loaded was determined spectrophotometrically at 228 nm. All the experiments were carried out in triplicate (n=3) (Liu et al., 2017). ME (%) = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} * 100
Table 3: In vitro mucoadhesion (wash-off) test

| Formulation code | Percent of microcapsules adhering at different times (h) |
|------------------|--------------------------------------------------------|
|                  | 0.5 | 1   | 2   | 3   | 4   |
| F1               | 75  | 47  | 15  | 0   | 0   |
| F2               | 83  | 59  | 23  | 7   | 0   |
| F3               | 87  | 71  | 35  | 21  | 5   |
| F4               | 91  | 79  | 61  | 27  | 7   |
| F4Ac             | 75  | 63  | 31  | 15  | 0   |
| F4C              | 71  | 55  | 27  | 11  | 0   |
| F4M              | 83  | 71  | 43  | 31  | 11  |
| F4P              | 79  | 67  | 35  | 25  | 5   |

Results obtained are presented as an average of 3 determinations.

Figure 4: FT-IR spectra of formulations

Swelling studies

Accurately weighed microcapsules (50 mg) were placed in a glass vial containing 10 mL of phosphate buffer pH 6.8 at 37±0.5°C in an incubator with occasional shaking and allowed to stand at room temperature for 6 hours. The microcapsules were removed, blotted with filter paper, and the swollen microcapsules were weighed. Each experiment was carried out in triplicate (n=3) (Clercq et al., 2019). The swelling index was obtained by using the following formula. \( Swelling\ index = \frac{(W_t - W_0)}{W_0} \times 100 \)

where \( W_0 \) and \( W_t \) are the initial weight of the micro-particles and weight of the micro-particles at time \( t \) respectively.

In-vitro drug-release studies

Dissolution study was carried out using a rotating basket method (Model TDT6P Electrolab, Mumbai). About 900 mL of the dissolution medium (0.5% w/v sodium lauryl sulfate in distilled water, pH 6.8)
was taken in a covered vessel, and the temperature was maintained at 37±0.5 °C. The speed of the paddle was set at 100 rpm. Prepared microcapsules containing drug equivalent to 10 mg was used for the study. The dissolution test was carried out by withdrawing 5 mL of dissolution media at specific time intervals and was replaced by the same amount of fresh medium. Samples were assayed at 228 nm for paclitaxel using the UV spectrophotometer. Each experiment was carried out in triplicate (n=3) (Achim et al., 2008).

**Mucoadhesion characteristics**

The muco-adhesive properties of microcapsules were evaluated by an in vitro adhesion testing method known as wash off method. Freshly excised piece of the intestinal mucosa (2 x 2 cm) from albino rat was mounted on to glass slides (3 x 1 inch) with cyanoacrylate glue. The glass slides were connected with suitable support to the arm of a USP tablet disintegrating test apparatus. About 25 microcapsules were spread onto the intestinal mucosa. When the disintegrating test machine was operated, the tissue specimen was given slowly in regular up and down movement in the test fluid (900 mL of simulated intestinal fluids) at 37±0.5°C contained in a one-litre vessel of the machine. At the end of 0.5 h, one hour, and subsequently at hourly intervals up to 6 h, the machine was stopped, and numbers of microcapsules still adhering to the tissue was calculated. The studies were carried out in triplicate (n=3) (Xu et al., 2019).

**Characterization studies**

**Fourier transform infrared (FTIR) Studies**

FT-IR studied the chemical compatibility between paclitaxel and the other formulation components (excipients). The FTIR spectra of moisture-free powdered samples of drug, excipients and prepared formulations were recorded using IR Affinity-1 FTIR spectrophotometer, Shimadzu, Japan. The samples were mixed with potassium bromide and compressed into a pellet before recording the spectra (Ahmad et al., 2014).

**Differential scanning calorimeter (DSC) studies**

DSC scans were performed on accurately weighed paclitaxel and formulations (Perkin Elmer, Singapore Make DSC-4000). Sealed and perforated aluminium pans were used for placing the samples. Temperature calibrations were performed using...
indium as standard. An empty pan was sealed in the same way as the sample was used as a reference. The samples were run at a scanning rate of 40°C/min from 40-300°C (Martins et al., 2014).

**Scanning electron microscope (SEM) analysis**

The particle size, shape, and surface morphology of microcapsules were examined by scanning electron microscopy. Microcapsules were fixed on aluminium stubs and coated with gold using a sputter coater SC 502, under vacuum (0.1 mmHg). The microcapsules were then analyzed by using SEM (Model LEICA S-430, London, UK) (Aukunuru et al., 2013).

**RESULTS AND DISCUSSION**

Microcapsules of paclitaxel with sodium alginate in a (drug: sodium alginate) ratio of 1:1, 1:2, 1:3 and 1:4 and with co-polymer (drug: sodium alginate: co-polymer) in a ratio of 1:2:2 were successfully prepared by ionotropic gelation process.

**Size of Microcapsules**

Microcapsules were found to be spherical, oblong, large and free-flowing. The sizes vary from one formulation to another. The particle size was in the range of 534 to 822µm. Nagarajan Sriram et al., obtained similar-sized microcapsules, working with pioglitazone hydrochloride using ionotropic external gelation technique (Sriram and Katakam, 2016). The size of microcapsules was increased with the incorporation of acacia, carbomer 941, povidone K-30 and macrogol (PEG 6000). The size was also reduced with higher levels of calcium chloride and reaction time. The results were depicted in Table 2.

**Drug content and microencapsulation efficiency**

The drug content and microencapsulation efficiency are given in Table 2. The drug content was found to be uniform in each formulation and could be reproducible in each batch of prepared microcapsules. The microencapsulation efficiency was in the range of 45.09–99.83% which is better as compared to the method of preparation of paclitaxel loaded poly(lactide-co-glycolide) microspheres by Zongrui Zhang et al., which gave an encapsulation efficiency of 92.82% (Zhang et al., 2018b). The microencapsulation efficiency was enhanced by the incorporation of co-polymers like acacia, carbomer 941, povidone K-30 and macrogol (PEG 6000). It was also observed that the entrapment efficiency was enhanced slightly with an increase in cross-linking time. In contrast, an increase in cross-linking concentration did not influence the drug-loading process.

**Swelling characteristics**

The swelling characteristics were presented as a swelling index in Table 2. The swelling property depends on the polymer concentration, ionic strength, as well as the presence of water. The dynamic process of mucoadhesion in-vitro occurs with optimum water content—overall hydration results in the formation of a wet, slippery mucilage without adhesion. The swelling index of prepared microcapsules was found in the range of 1200-2666 at the end of 3 h. The result showed that the swelling index was enhanced by the incorporation of acacia, whereas the ratio reduced when combined with other co-polymers. This result was similar to the results obtained by Patil et al., who worked on salbutamol using methylcellulose, sodium carboxymethylcellulose, carbopol and hydroxyl propyl methyl cellulose where they obtained microcapsules with the high swelling index for hydroxypropyl methylcellulose and less for methylcellulose (Rao et al., 2010).

**Drug release characteristics**

The drug release characteristics of the prepared formulations were presented in Figures 1 and 2. Paclitaxel release from microcapsules was slow, spread over extended periods, and depended on the composition of the coat. Microcapsules of alginate-acacia gave relatively fast release when compared to others. The order of increasing release rate observed with various microcapsules was alginate-acacia<alginate-povidone<alginate-carbomer<alginate-macrogol. It indicates that alginate-acacia microcapsules gave relatively higher release (t<sub>50%</sub>, 1.5 h) than alginate-macrogol (t<sub>50%</sub>, 1.8 h) microcapsules. Kim CK et al. also reported similar findings (Chong-Kook et al., 1994). The concentrations of calcium chloride have little influence on the release of different concentration levels, namely 20 and 30% w/v solutions. However, a minimum concentration of 10% w/v solution of calcium chloride was found sufficient. Prepared microcapsules alginate (F4), alginate-acacia (F4Ac), alginate-carbomer (F4C), alginate-macrogol (F4M), alginate-povidone (F4P) were compared for controlled release pattern of the drug. The per cent drug release of microcapsules follows the order F4Ac>F4P>F4M>F4C>F4. The drug release was maximum of 99.5% with F4Ac formulation. Jagadeesh G Hiremath et al. prepared paclitaxel loaded poly (caprolactone) microspheres by solvent evaporation method and found that the cumulative per cent drug release was 62.54±1.6 at the end of 30 days. It shows that the ionic gelation method could be a better choice as compared to solvent
evaporation method (Hiremath and D, 2010). Hence, controlled release pattern of alginate-acacia microcapsules (F4Ac) was comparable to the commercially available dosage form of paclitaxel. In the case of the currently marketed intravenous drug formulations, paclitaxel injection is administered intravenously over three hours at a dose of 175 mg/m² followed by cisplatin at a dose of 75 mg/m² or paclitaxel injection administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin at a dose of 75 mg/m² (Martín, 2015). The result of the in vitro drug release showed that there was no significant change in percentage drug content, and the microcapsules could release the drug periodically for four hours in a controlled manner.

**Mucoadhesion characteristics**

The microcapsules exhibited suitable mucoadhesive property in the in-vitro wash-off test. The results are given in Table 3. The strength for mucoadhesion was found to be directly proportional to the concentration of polymer. Although the combination of polymers attained the maximum value of muco-adhesive strength, significant muco-adhesive strengths were also shown by individual polymers in simulated intestinal fluids. The optimized formulation F4M showed considerable higher muco-adhesive strength as compared to other formulations with a muco-adhesive time over more than 4 hours (Pal and Nayak, 2012).

**Scanning electron microscope (SEM) studies**

The morphological characterization revealed that the alginate microcapsules (F4) were spherical. The surface of the microcapsules was almost smooth, free from pores and deposits. The SEM photographs of alginate-acacia microcapsules (F4Ac) showed that microcapsules were nearly spherical, as shown in Figure 3. The surface was smooth but contained longitudinal depression, whereas the F4Ac resulted in better morphological structure and more smooth surface as compared to the F4 formulation (Zhang et al., 2018a).

**Fourier transforms infrared (FTIR) Studies.**

In paclitaxel FTIR spectrum, major peaks were obtained at 3497.09 cm⁻¹, along with broad-band in the region of 3600-3100 cm⁻¹ which may be attributed to the presence of –NH and –OH stretching due to secondary amine and hydroxyl groups (D and Prabhakar, 2017). The peak at 3035.12 cm⁻¹ indicates the presence of C-H stretching in aromatic hydrocarbons. The peak can detect the presence of C-H stretching due to –CH₂ and –CH₃ of aliphatic chain at 2954.11 cm⁻¹. The carbonyl group, C=O stretching peak at 1732.15 cm⁻¹ may be attributed to carboxylic ester group and C=O stretching peak at 1647.28 cm⁻¹ to amide group. The peak at 1073.43 cm⁻¹ indicates the presence of C-O-C coupling interaction and peak at 710.80 cm⁻¹ may be attributed to out of plane deformation of a methylene group. Compatibility of paclitaxel with excipients was studied using polymers such as sodium alginate, povidone, carbomer, macrogol and gum acacia. The FTIR spectra of the prepared microcapsules (F4Ac, F4P, F4C, F4M) showed characteristic peaks for drug and excipients with no significant shift in positions indicating that there was no chemical interaction between the drug and polymers, thus confirming the drug compatibility with the excipients. The FT-IR spectra are showed in Figure 4 shows that A: FTIR spectra of F4Ac,Paclitaxel,Sodium alginate, Acacia presented from top to bottom respectively B: FTIR spectra of F4M,Macrogol,Paclitaxel, Sodium alginate presented from top to bottom respectively C: FTIR spectra of F4P,Povidone, Paclitaxel, Sodium alginate presented from top to bottom respectively D: FTIR spectra of F4C, Carbomer, Paclitaxel, Sodium alginate presented from top to bottom respectively.

**Differential scanning calorimeter (DSC) studies**

The DSC thermograms of paclitaxel showed a characteristic peak at 223.83 °C, which corresponds to the melting point of the drug (Mu and Feng, 2001). The peak started at 213.84 °C and ended at 231.03 °C with an area of 187.172 mJ, height of 11.0802 mW and ΔH value of 50.5869 l/g. The formulations F4Ac, F4P, F4C showed characteristic peaks for drug and excipients with a peak shift towards lower temperature region, which may be due to the presence of additives. The formulation F4M showed small peaks around 223.83 °C, which could be due to less drug content in the formula. DSC thermograms of different polymers and prepared microcapsules with their peak areas are showed in Figure 5 shows that A: DSC thermogram of F4Ac, B: DSC thermogram of F4C, C: DSC thermogram of F4P, D: DSC thermogram of F4M.

Muco-adhesive polymers as carriers that sustain the drug release seem to be a promising polymer for colonic delivery of a drug(s) (Sudheer, 2018). Among such polymers, sodium alginate is widely used natural polymer for mucoadhesion, but it is unable to effectively prevent the drug release during transit through upper gastrointestinal tract (Sachan et al., 2009). Sodium alginate polymers are cross-linked using acacia, povidone, macrogol and carbomer as a co-polymers, to overcome this difficulty.
CONCLUSIONS

The above research was unique as the effect of co-polymers such as acacia, povidone, macrogol and carbomer along with the primary polymer sodium alginate was studied to obtain an optimized muco-adhesive microcapsule of paclitaxel. The results revealed that alginate-acacia microcapsule gave relatively higher percent release than alginate-carbomer. The concentrations of calcium chloride and reaction time exposure have little effects on the release rate. The controlled-release pattern of alginate-acacia microcapsule was observed to release paclitaxel for six h. Microcapsules prepared with alginate-acacia and alginate-povidone was found good with respect to release, swelling ratio, mucoadhesion, and morphological characteristics. Hence, these are suitable carriers for oral controlled release of paclitaxel.

ACKNOWLEDGEMENT

Authors deeply acknowledge the Head, Post Graduate Department of Zoology, Berhampur University and the Director, Royal College of Pharmacy and Health Sciences, Berhampur for providing the necessary laboratory facilities. Further, we are deeply indebted to Neon Laboratories, Naprod Life Sciences, Mumbai for providing the drug in the test as gift samples.

Funding Report None
Conflict of interest None

REFERENCES

Achim, M., Tomuta, I., Vlase, L., Iuga, C., Moldovan, M., Leucuta, S. E. 2008. Paclitaxel-loaded poly(lactic-co-glycolic acid) microspheres: preparation and in vitro evaluation. Journal of Drug Delivery Science and Technology, 18(6):410–416.

Ahmad, J., Mir, S. R., Kohli, K., Chuttani, K., Mishra, A. K., Panda, A. K., Amin, S. 2014. Solid-Nanoemulsion Preconcentrate for Oral Delivery of Paclitaxel: Formulation Design, Biodistribution, and Scintigraphy Imaging. BioMed Research International, 2014:1–12.

Al-najjar, B. Y., Hussain, S. A. 2017. Chitosan Microspheres For The Delivery Of Chemotherapeutic Agents: Paclitaxel As A Model. Asian Journal of Pharmaceutical and Clinical Research, 10(8):15–15.

Aukunuru, J., Goverdhan, P., Habibuddin, M., Ramchander, T., Shiny, J. 2013. Development and evaluation of a novel biodegradable sustained release microsphere formulation of paclitaxel intended to treat breast cancer. International Journal of Pharmaceutical Investigation, 3(3):119–119.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., Jemal, A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68(6):394–424.

Chong-Kook, K., Mi-Jung, K., Kyoung-Hee, O. 1994. Preparation and evaluation of sustained release microspheres of terbutaline sulfate. International Journal of Pharmaceutics, 106(3):213–219.

Clercq, K. D., Xie, F., Wever, O. D., Descamps, B., Hoorens, A., Vermeulen, A., Ceelen, W., Vervaet, C. 2019. Preclinical evaluation of local prolonged release of paclitaxel from gelatin microspheres for the prevention of recurrence of peritoneal carcinomatosis in advanced ovarian cancer. Scientific Reports, 9(1):14881–14881.

D. M., Prabhakar, V. K. 2017. Polyethylene Glycol Conjugates Of Paclitaxel As Prodrugs By Simple Technique Such As Solvent Evaporation. International Research Journal of Pharmacy, 8(6):109–112.

Gu, W., Zou, H., Li, L., Carcedo, I. G., Xu, Z. P., Monteiro, M. 2016. Synergistic inhibition of colon cancer cell growth with nanoemulsion-loaded paclitaxel and PI3K/mTOR dual inhibitor BEZ235 through apoptosis. International Journal of Nanomedicine, 11:1947–1947.

Haggar, F., Boushey, R. 2009. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. Clinics in Colon and Rectal Surgery, 22(04):191–197.

Hiremath, J., D. V. 2010. Preparation and in vitro characterization of paclitaxel-loaded injectable microspheres. Asian Journal of Pharmaceutics, 4(3):205–211.

Jin, J. F., Zhu, L. L., Chen, M., Xu, H. M., Wang, H. F., Feng, X. Q., Zhou, Q. 2015. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. Patient Preference and Adherence, 9:923–942.

Kruijtzer, C. M. F., Boot, H., Beijnen, J. H., Lochs, H. L., Parnis, F. X., Planting, A. S. T., Pelgrims, J. M. G., Williams, R., Mathôt, R. A. A., Rosing, H., Schot, M. E., van Tinteren, H., Schellens, J. H. M. 2003. Weekly oral paclitaxel as first-line treatment in patients with advanced gastric cancer. Annals of Oncology, 14(2):197–204.

Liu, K., Chen, W., Yang, T., Wen, B., Ding, D., Keidar, M., Tang, J., Zhang, W. 2017. Paclitaxel and quercetin nanoparticles co-loaded in
microspheres to prolong retention time for pulmonary drug delivery. *International Journal of Nanomedicine*, Volume 12:8239–8255.

Martín, M. 2015. Nab-Paclitaxel dose and schedule in breast cancer. *Breast Cancer Research*, 17(1).

Martins, K. F., Messias, A. D., Leite, F. L., Duek, E. A. 2014. Preparation and characterization of paclitaxel-loaded PLDLA microspheres. *Materials Research*, 17(3):650–656.

Menon, T. V., Sajeeth, C. I. 2013. Formulation and evaluation of sustained release sodium alginate microbeads of carvedilol. *Research Journal of Pharmacy and Technology*, 6(4):392–397.

Mu, L., Feng, S. S. 2001. Fabrication, characterization and in vitro release of paclitaxel (Taxol®) loaded poly (lactic-co-glycolic acid) microspheres prepared by spray drying technique with lipid/cholesterol emulsifiers. *Journal of Controlled Release*, 76(3):239–254.

Paclitaxel 2017. Different brand names of Paclitaxel. *Med India*.

Pal, D., Nayak, A. K. 2012. Novel tamarind seed polysaccharide-alginate mucoadhesive microspheres for oral gliclazide delivery: in vitro–in vivo evaluation. *Drug Delivery*, 19(3):123–131.

Rao, R. G., Hiremath, D., Patil, P. 2010. Preparation and characterization of mucoadhesive microcapsules of salbutamol sulfate. *Asian Journal of Pharmaceutics*, 4(2):141–141.

Sachan, S. P. N. K., Jha, A., Bhattacharya, A. 2009. Sodium alginate: the wonder polymer for controlled drug delivery. *Journal of Pharmacy Research*, 2(8):1191–1199.

Sarkar, T., Ahmed, A. B. 2016. Development And In-Vitro Characterisation Of Chitosan Loaded Paclitaxel Nanoparticle. *Asian Journal of Pharmaceutical and Clinical Research*, 9(9):145–145.

Sharma, N., Madan, P., Lin, S. 2016. Effect of process and formulation variables on the preparation of parenteral paclitaxel-loaded biodegradable polymeric nanoparticles: A co-surfactant study. *Asian Journal of Pharmaceutical Sciences*, 11(3):404–416.

Sriram, N., Katakam, P. 2016. Formulation and Evaluation of Mucoadhesive Microspheres of Pioglitazone Hydrochloride Prepared by Ionotropic External Gelation Technique. *Journal of Encapsulation and Adsorption Sciences*, 06(01):22–34.

Sudheer, P. 2018. Mucoadhesive Polymers: A Review. *Journal of Pharmaceutical Research*, 17(1):47–55.

Surapaneni, M. S., Das, S. K., Das, N. G. 2012. Design-