

# Statistical Approach in Designing, Formulation and Optimization of Paclitaxel Loaded Mucoadhesive Microcapsules

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**ABSTRACT:** The aim of this research work is to formulate mucoadhesive microcapsule of paclitaxel for the treatment of intestinal cancer and to study the effect of polymers on controlled release characteristics of microcapsules. Statistical design expert version 6.0.8 software was used to prepare microcapsules by ionic gelation method. Formulation containing acacia and sodium alginate resulted in 99.5% *in vitro* drug release with an encapsulation efficiency of 98.26%. The *in vitro* drug release studies indicate that the optimized formulation follows Hixson-Crowell model. The *n*-value of all the formulations lies in a range of 0.5-0.8 indicates non-Fickian transport mechanism. The microcapsules were found to release the drug more than 60% within 4-5 hours of time which could be comparable with 3 hours of intravenous infusion of standard marketed formulations and can be suitably replaced as an oral dosage form for better patient compliances.

**KEYWORDS:** paclitaxel, mucoadhesive microcapsules, effect of polymer, ionic gelation method.

## I. INTRODUCTION

The present study is aimed to develop a dosage form of anticancer drug which can be easily adopted by industry to formulate a marketable dosage form with enhanced efficacy and cost effective for patients compared to most of the available marketed drugs. The approach to formulate targeted drug delivery system may reduce the dose of drug to produce similar therapeutic effect, which in turn reduces the cost of unit dosage form. As many drugs exert prolonged therapeutic effect, if they remain in systemic circulation for a longer period of time. Mucoadhesive microcapsules of paclitaxel are proposed in the present work for release of the drug for a prolonged period of time in a controlled manner. The research work aims to find the effect of different polymers and their proportions on drug release characteristics or its pattern. The other properties like swelling characteristics, mucoadhesion properties, entrapment efficiency, and percent drug loading were analyzed to obtain the best formulation with optimized characteristics.

## II. RELATED WORK

Mucoadhesive microcapsules are the better choice of dosage forms compared to *i.v.* infusion or bolus injections to sustain the drug for a longer period of time [1]. Cell line study reveals that many anticancer drugs are more effective with a longer exposure time [2]. Paclitaxel could be used orally along with cyclosporine A as first-line treatment in patients with advanced gastric cancer [3]. Hence the study was aimed to encapsulate an anticancer drug paclitaxel in mucoadhesive microcapsule to target intestinal cancer with a controlled release of drug for a longer period of time. Most of the drugs have limitations based on their physicochemical and pharmacological characteristics. Paclitaxel was selected as a prototype, as it is more potent when compared to other drugs for intestinal cancer.

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Paclitaxel is administered through intravenous route only with nineteen different brand names and with a three weekly repeated dosage regimen, which incur huge cost to patient in terms of treatment [4]. This could be overcome by formulation approach of paclitaxel into oral dosage form. As paclitaxel is a high molecular weight compound, its bioavailability can be enhanced by reducing its size to micro or nano scale and target the drug to treat intestinal cancer, which is the third and fourth most common cancer globally [5].

### III. MATERIAL AND METHODS

#### Materials

Paclitaxel was obtained as gift sample from Neon Laboratories Pvt. Ltd. and Naprod life science pvt. Ltd., Boisor, India. Polymers such as acacia, carbomer 941, hypromellose K-15, methyl cellulose, povidoneK-30, macrogol (PEG 6000) and gelatin were obtained as gift sample from Ipca Laboratories Ltd., Athal, India. Sodium alginate, chitosan, calcium chloride were procured from Thomas Baker, Merck and Loba Chemie Pvt. Ltd. All other chemicals are of analytical grade.

#### Methods

##### Statistical design:

Statistical design expert version 6.0.8 was used to design and optimize the formulation. 30 mg of drug was taken in each formulation with different ranges of polymer concentration such as sodium alginate (4-6 % w/v), acacia, carbomer, macrogol, povidone (each in range of 0-2 % w/v). A total of 17 formulations were prepared by using factorial design and optimized based on evaluation parameters.

##### Preparation of microcapsules

Microcapsules were prepared by ionic gelation technique using different polymer combinations. Sodium alginate and other polymers specified in different proportions for different formulations were dispersed in 20 ml of distilled water with the help of mechanical stirrer to form a homogeneous solution. Paclitaxel (30 mg), was dissolved in 2 ml of ethanol by sonicator and added to the polymer solution and mixed thoroughly to get a uniform dispersion. The resulting dispersion was then added manually drop wise into calcium chloride solution 10% w/v through a syringe with a needle size number 24. A curing time of about 30 minutes was allowed for each formulation and then filtered through Whatman filter paper and washed with distilled water. The microcapsules were dried over night at room temperature and evaluated for different characteristic properties [6]. The formulae used for preparing microcapsules were presented in **Table I- II**

**Table I: Formulations without drug for polymer selection.**

Formulations	Polymer	(Sodium alginate : polymer)	Yield(g)	Observations
T1	Gelatin	4:1		Gelatin did not mix with sodium alginate dispersion
T2	Acacia	4:1	1.952	Spherical shaped microcapsules obtained
T3	Povidone	4:1	1.027	Microcapsules obtained with small tails and are sticky to each other.
T4	Chitosan	4:1		Chitosan did not mix with sodium alginate dispersion
T5	Macrogol	4:1	0.887	Irregular shaped microcapsules obtained
T6	Hypromellose	4:1	0.570	Bubbles produced while adding hypromellose and dispersion become highly viscous.
T7	Carbomer	4:1	1.113	Spherical shaped microcapsules obtained

## International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

**Table II: Formula for preparation of paclitaxel encapsulated microcapsules.**

Formulation	Drug (Paclitaxel) (mg)	Sodium alginate (%)	Acacia (%)	Carbomer (%)	Macrogol (%)	Povidone (%)
F1	30	6.0	0	2.0	0	2.0
F2	30	6.0	0	0	0	0
F3	30	4.0	0	2.0	0	0
F4	30	4.0	0	2.0	2.0	2.0
F5	30	6.0	2.0	2.0	0	0
F6	30	5.0	1.0	1.0	1.0	1.0
F7	30	4.0	2.0	2.0	0	2.0
F8	30	6.0	0	0	2.0	2.0
F9	30	4.0	2.0	2.0	2.0	0
F10	30	4.0	2.0	0	2.0	2.0
F11	30	4.0	2.0	0	0	0
F12	30	6.0	0	2.0	2.0	0
F13	30	6.0	2.0	2.0	2.0	2.0
F14	30	6.0	2.0	0	2.0	0
F15	30	6.0	2.0	0	0	2.0
F16	30	4.0	0	0	0	2.0
F17	30	4.0	0	0	2.0	0

### **Estimation of drug content by UV- Vis Spectroscopy:**

The UV-Vis Spectrophotometer model UV-1800, Shimadzu was used to obtain calibration curve of pure drug paclitaxel. The drug was dissolved in methanol followed by making serial dilutions in a range of 2-20 ppm with 0.5% w/v sodium lauryl sulphate (SLS) in water [7]. The prepared microcapsules 10 mg were sonicated in 25 ml of 0.5% w/v SLS for 30 min and the supernatant liquid after filtration through micropore filter was used for estimation of drug content.

### **Fourier transform infrared analysis (FT-IR):**

The FT-IR spectral measurements of pure paclitaxel, polymers and prepared formulations were obtained at ambient temperature using IR Affinity-1 FT-IR spectrometer (Shimadzu, Japan). About 5 mg of samples were mixed with 95 mg of micronized dried IR grade Potassium bromide (KBr). All the spectra acquired scans between 4000 cm<sup>-1</sup> to 400 cm<sup>-1</sup> and recorded in the transmittance mode using IR solution software [8].

### **Thermal analysis (DSC):**

The thermograms of pure drug paclitaxel, polymers and prepared formulations were obtained using differential scanning calorimeter (Perkin Elmer, Singapore make DSC-4000). Samples were weighed (3-5 mg) and placed in non-hermetically sealed aluminum pan. The analysis was performed using nitrogen gas with flow rate of 20 ml/min and heating at a constant heating rate of 40°C/min in the range of 40- 300 °C [9].

### **Evaluation of microcapsules**

#### **Percentage yield:**

The prepared and dried microcapsules of all formulations were weighed accurately. The measured weight was divided by the total amount of all the polymers and drug used in respective formulations to obtain the total percentage yield. It was calculated using following formula

Percentage Yield = Weight of final product (microcapsules) X100/ Weight of initial raw materials

# International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

## **Entrapment efficiency:**

The Percent drug loading and entrapment efficiency was determined by the reported method with a slight modification [10]. The microcapsules (10 mg) was allowed to disintegrate in 25 ml of 0.5% w/v sodium lauryl sulphate solution using sonicator at 125 W for 30 minutes. The dispersion was then filtered through Whatman filter paper (0.45 mm). The drug content of the filtrate was determined by UV-Vis spectrophotometer at 228 nm.

Entrapment efficiency (%) = Actual amount of drug in microcapsules X100/Theoretical amount of drug added initially.

Drug Loading (%) = Weight of active drug loaded in microcapsules X100/ Total weight of microcapsules taken initially

## **In vitro wash off test:**

The mucoadhesion property of the prepared microcapsules was studied by *in vitro* wash off test. The test was performed in both 0.1 N HCl and phosphate buffer pH 6.8. The freshly excised piece of goat intestinal mucosa (20 x 30 mm) was mounted onto glass slide with cyanoacrylated glue. About 20 numbers of microcapsules were spread onto each wet rinsed tissue specimen and immediately thereafter the slides were hung onto the arm of a USP tablet disintegration test apparatus. The tissue specimen was placed in a vessel containing one liter fluid at 37°C and given a slow and regular up-down movement. The apparatus was stopped at predetermined time interval and the number of microcapsules still adhered to the tissue was counted. Each determination was made in triplicate and the adhesion percentage was calculated by the following formula [11].

Mucoadhesion (%) = Number of microcapsules adhered X100/Number of microcapsules applied

## **Swelling index:**

The swelling of microcapsules was studied in phosphate buffer pH 6.8. 0.5 ml of microcapsule bed was soaked in 5 ml of 0.1 N HCl and phosphate buffer pH 6.8 separately in 10 ml measuring cylinder. The volume of microcapsules was determined after 12 hrs. Swelling index was calculated using following formula [12].

Swelling index = (Weight of swelled microcapsules- weight of dried microcapsules) X100/ Weight of dried microcapsules.

## **In vitro drug release study:**

The release of paclitaxel was determined using USP dissolution test apparatus I. 100 mg of microcapsules were placed in basket and allowed to rotate at 100 rpm in 500 ml of dissolution medium containing 0.5% sodium lauryl sulphate in distilled water [13]. This is carried out for 6 hours at a constant temperature of 37 ± 0.5 °C. 5 ml aliquots were withdrawn at predetermined time intervals with immediate replacement of 5 ml of fresh medium to maintain sink conditions. The samples were analyzed by UV-Vis spectrophotometer to estimate the percentage drug release [14].

Drug release (%) = Concentration at specified time point X100/ Concentration at complete release

## **Mechanism of drug release**

The results obtained from *in-vitro* release study were fitted into mathematical models such as Zero-order kinetic model (plot of cumulative percent drug released versus time), First-order kinetic model (plot of log cumulative percent drug remaining versus time), Higuchi's model (plot of cumulative percent drug released versus square root of time), Korsmeyer-peppas equation (plot of log cumulative percent drug released versus log time), Hixson-Crowell model (root of drug percentage remaining in matrix versus time). The R<sup>2</sup> values and n values obtained in each model for all the formulations were compared to study the mechanism for the release rate kinetics of the mucoadhesive microcapsules [15].

## IV. RESULTS

### *UV-Vis spectral analysis*

The UV analysis of paclitaxel showed maximum absorbance at 228 nm. The absorbance of different concentrations of solution of drug with methanol followed by dilutions with 0.5% w/v of SLS in distilled water in a range of 2-20 parts per million (ppm) resulted a linear plot with r<sup>2</sup> value 0.998. The calibration curve of paclitaxel is given in **Figure 1**.

# International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

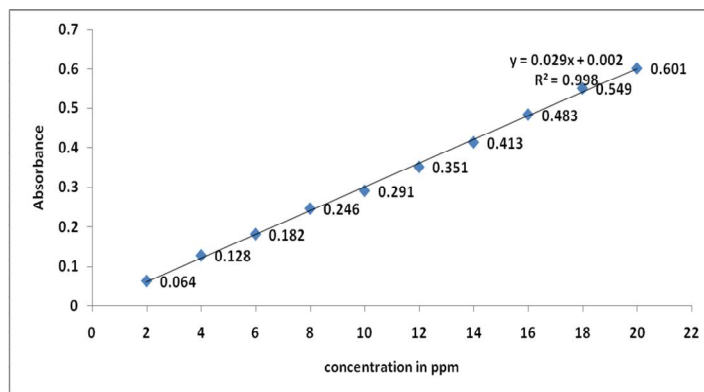


Fig 1: Calibration curve of paclitaxel

### Fourier transform infrared analysis

Paclitaxel showed characteristic sharp spiked peaks at  $3497.09\text{ cm}^{-1}$  along with broadening in the region of  $3600\text{-}3100\text{ cm}^{-1}$  which may be attributed to the presence of  $\text{-NH}$  and  $\text{-OH}$  stretching due to secondary amine and hydroxyl groups. The peak at  $3035.12\text{ cm}^{-1}$  indicates the presence of  $\text{C-H}$  stretching in aromatic hydrocarbons. The presence of  $\text{C-H}$  stretching due to  $\text{-CH}_3$  and  $\text{-CH}_2\text{-}$  of aliphatic chain can be detected by the peak at  $2954.11\text{ cm}^{-1}$ . The carbonyl group,  $\text{C=O}$  stretching peak at  $1732.15\text{ cm}^{-1}$  may be attributed to carboxylic ester group and  $\text{C=O}$  stretching peak at  $1647.28\text{ cm}^{-1}$  to amide group. The peak at  $1073.43\text{ cm}^{-1}$  indicates presence of  $\text{C-O-C}$  coupling interaction and peak at  $710.80\text{ cm}^{-1}$  may be attributed to out of plane deformation of 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 (F2, F3, F5, F8, F10, F11 and F14) showed characteristic peaks for drug and excipients with no significant shift in positions whereas the formulations such as F15, F16 and F17 showed a significant change in the peak positions and peak shape. The overlay FT-IR spectra of pure drug, polymers and prepared microcapsules are shown in **Figures 2 and 3**.

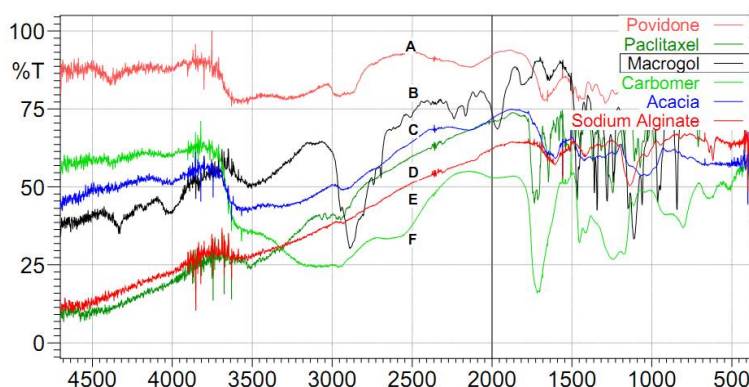


Fig 2: FT-IR spectra overlay of pure drug (paclitaxel) and polymers. A- povidone, B- macrogol, C- Acacia, D- paclitaxel, E- sodium alginate, F- carbomer.

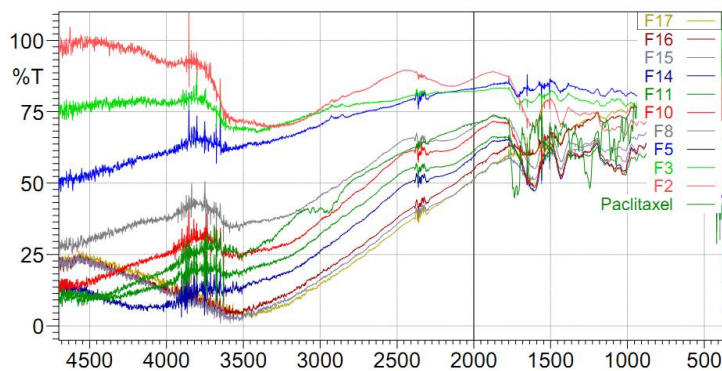


Fig 3: FTIR spectra overlay of pure drug (paclitaxel) and formulations.

### Thermal analysis (DSC)

The DSC thermograms of paclitaxel showed a characteristic peak at 223.83°C which corresponds to the melting point of the drug. The peak started at 213.84°C and ended at 231.03°C with area of 187.172 mJ, height of 11.0802 mW and  $\Delta H$  value of 50.5869 J/g. The Formulations F3, F5, F8, F11, F15 and F16 showed characteristic peaks for drug and excipients with a peak shift towards lower temperature region which may be due to the presence of additives. Other formulations 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 shown in **Figures 4 and 5**.

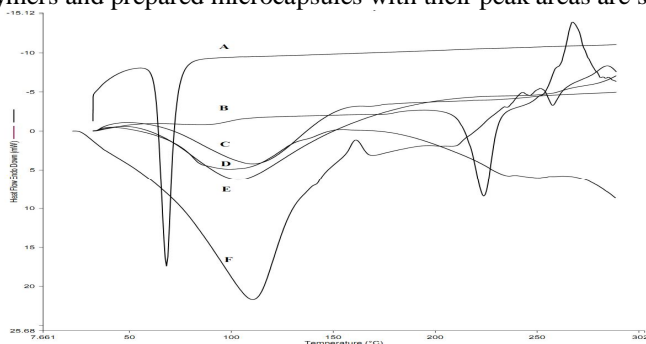


Fig 4: DSC thermogram of pure drug (paclitaxel) and polymers. A-macroglol, B- paclitaxel, C- povidone, D- carbomer, E- acacia, F- sodium alginate.

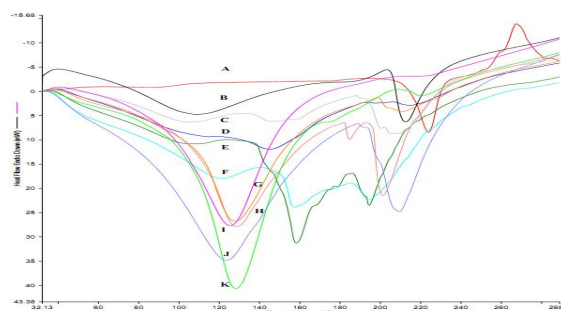


Fig 5: DSC thermogram of pure drug (paclitaxel) and formulations. A- paclitaxel, B- F8, C- F16, D- F2, E- F3, F- F5, G- F17, H- F15, I- F10, J- F 11, K- F14.



## International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

The results obtained for evaluation parameters such as percent drug loading and encapsulation efficiency, *in vitro* wash off test, *in vitro* drug release using UV-Vis spectrophotometer and the swelling index obtained for the prepared microcapsules are summarized in **Table III**.

The *in vitro* drug release studies indicate that the formulations F2, F3, F5, F8, F10 and F14 fit into Higuchi model where as formulations F11, F15, F16 and F17 fit into Hixsonn- Crowell model. The n- value of all the formulations lies in a range of 0.5-0.8 indicating non-fickian transport mechanism. The R<sup>2</sup> values and n- values of prepared formulations following different kinetic models are given in **Table IV**.

**Table III: Evaluation of prepared microcapsules.**

Formulation	Microcapsules characteristics	Yield (%)	Encapsulati on efficiency (%)	Drug Loading (%)	Swelling index	Dissolution (% drug release)	Mucoadhesion (%)
F1	Not obtained	-	-	-	-	-	-
F2	Obtained	94.63	94.32	2.431	1342	64.23	72
F3	Obtained	97.39	45.09	1.129	2666	69.65	92
F4	Not obtained	-	-	-	-	-	-
F5	Obtained	52.41	3.67	0.103	2358	66.79	88
F6	Not obtained	-	-	-	-	-	-
F7	Not obtained	-	-	-	-	-	-
F8	Obtained	57.14	81	2.095	2192	74.27	86
F9	Not obtained	-	-	-	-	-	-
F10	Obtained	43.33	72.67	2.422	1892	93.46	80
F11	Obtained	90.73	98.26	2.776	1278	99.5	78
F12	Not obtained	-	-	-	-	-	-
F13	Not obtained	-	-	-	-	-	-
F14	Obtained	62.02	82.84	1.974	1568	90.1	78
F15	Obtained	71.03	99.83	2.181	1956	100.21	84
F16	Obtained	81.06	96.54	2.905	1200	97.23	76
F17	Obtained	80.49	94.73	2.871	1438	85.44	80

**Table IV: Drug release kinetic models.**

Formulations	Zero order (R <sup>2</sup> )	First order (R <sup>2</sup> )	Hixson-Crowell model (R <sup>2</sup> )	Korsmeyer-Peppas model (n)	Higuchi model (R <sup>2</sup> )
F2	0.841421	0.841421	0.893053	0.705764	0.970932
F3	0.827397	0.827397	0.902398	0.692256	0.97327
F5	0.788644	0.788644	0.847976	0.707646	0.946519
F8	0.923839	0.923839	0.969469	0.705142	0.987925
F10	0.82998	0.82998	0.953616	0.745383	0.967677
F11	0.808769	0.808769	0.969033	0.519254	0.949224
F14	0.91726	0.91726	0.981452	0.743178	0.990896
F15	0.740874	0.740874	0.96562	0.759866	0.912152
F16	0.818366	0.818366	0.968166	0.752162	0.966174
F17	0.928585	0.928585	0.978744	0.741662	0.978288

The percent of drug released with respect to time are shown in **Figures 6**. Formulations F10,F11,F14,F15 and F16 releases more than 90% of drug whereas other formulations releases drug around 60-80%

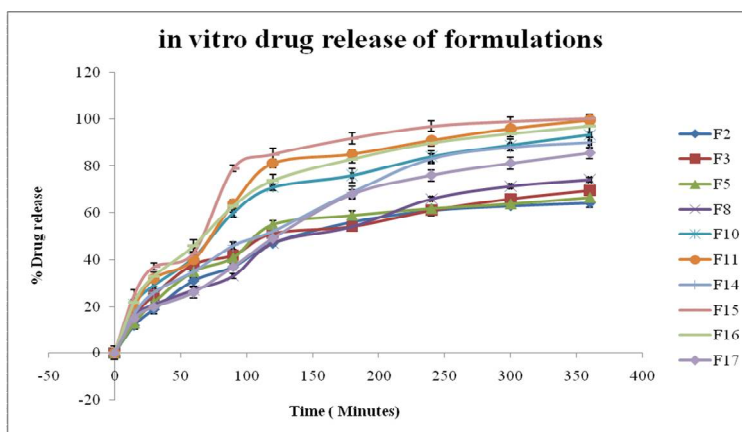


Fig 6: in vitro drug release profile of microcapsules.

## V. DISCUSSION

Microcapsules were successfully prepared by ionic gelation method. Seven trials (T1 to T7) were conducted for selecting polymers to be used along with sodium alginate by keeping concentration of polymer to 5%w/v in a proportion of sodium alginate to polymer (4:1). Microcapsules were obtained with acacia, povidone, macrogol and carbomer with a maximum yield of 1.952% with acacia. Spherical shaped microcapsules were obtained by using acacia and carbomer. Povidone imparts sticky characteristics whereas macrogol increases the irregularity in the shape of microcapsules. Gelatin and chitosan did not mix with sodium alginate dispersion whereas hypromellose resulted in a very viscous dispersion and hence, these polymers were not used further in the study. These four polymers (acacia, carbomer, macrogol and povidone) were taken in different proportions with sodium alginate to prepare paclitaxel encapsulated microcapsules. Microcapsules could not be obtained when carbomer and povidone were taken all together in the formulations. This combination resulted in highly viscous dispersion which rendered it difficult to drop out from the needle while preparing microcapsules. Combination of acacia and carbomer results in sticky microcapsules. Flat or disc shaped microcapsules were obtained with an increase in the dropping height. The increase in viscosity of drug polymer mixture and high speed of rotation of teflon bead in magnetic stirrer resulted in tailing and irregular shape of microcapsules. Out of the seventeen random designs (F1 to F17) only ten formulations could be prepared successfully. The effect of polymers on the evaluation characteristics of microcapsules are summarized in Table IV. Based on the above observations we can predict that the formulation F11 which contains paclitaxel along with sodium alginate and acacia was considered as the best formulation among others with encapsulation efficiency of 98.26 %, drug loading of 2.776%, swelling index of 1278 and 99.5% drug release.

## VI. CONCLUSIONS

Paclitaxel being a most potent drug could be encapsulated into mucoadhesive microcapsules for treatment of intestinal cancer. Though the drug is water insoluble, an attempt to prepare mucoadhesive microcapsules seems to be successful with different polymer combinations. The microcapsules (F11) prepared by using sodium alginate and acacia resulted in 99.5% in vitro drug release with an encapsulation efficiency of 98.26% was considered as best formulation with swelling index of 1278, 2.776% drug loading capacity. As the process loss is not significant, this method could be easily adopted for commercial batch preparation. Povidone enhances percent drug release, encapsulation efficiency and percent drug loading but decreases swelling and mucoadhesion characteristics. Carbomer decreases the percent drug release. Acacia enhances encapsulation efficiency and percent drug loading. Macrogol enhances percent drug release, encapsulation efficiency and percent drug loading but decreases the yield. Sodium alginate alone could be sufficient to prepare microcapsules but to enhance the drug release, entrapment efficiency and mucoadhesion characteristics the different polymers can be used in a definite proportion to yield an optimized formulation. The microcapsules were



# International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

found to release the drug completely within 4-5 hours which could be comparable with 3 hours of intravenous infusion of standard marketed formulations. Hence, microcapsules as oral dosage form can suitably replace the intravenous infusion for better patient compliance.

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