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FORMULATION DEVELOPMENT OF CURCUMIN LOADED SOLID LIPID NANOPARTICULATE ORAL JELLIES

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Keywords:

OSMF, Curcumin, HPβCD, Solubility, SLN's

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ABSTRACT

Oral submucous fibrosis (OSMF) has been reported in 33% to 40%of Indian population due to an excessive usage of gutkha, tobacco, pan masalas and areca nut. In OSMF due to the stiffness in oral mucosa a difficulty in opening the mouth and no effective treatment has been reported. Therefore, a need to develop an oral formulation that would dissolve slowly in the oral cavity without causing any irritation or inflammation is required. The reported literature reveals the advantage of Solid lipid nanoparticles with respect to toxicity, stability, biocompatibility and scale up issues. The surfactant coated nanoparticles have been reported to cause successful transportation of drugs across the lipid membrane. The medicated nanoparticulated Jelly containing inclusion complex of Cu-HPβ-CD SLNs has gained acceptance as a drug delivery due to an ease and convenience in administration without water. Thats why attempt has been made to formulate and evaluate Curcumin- HPβ-CD based medicated nanoparticulated jelly and focus on an improvement of its aqueous solubility. Saturation solubility of Cu had increased to (0.085mg/ml) that is 300 folds as compared to the pure Cu sample (0.00027mg/ml), indicating an improvement in saturation solubility after complexation with HPβCD. The SLN successfully showed % EE of 83.46 ± 0.04 %. The formulation of Jelly containing inclusion complex of Curcumin HPβCD SLN's using different concentration of jellying agent pectin. All batches were evaluated for drug content, pH, consistency, viscosity and gel strength, *In-vitro* dissolution studies. The batch showed 70.14% ± 0.25% drug release after 7 hour. Hence was selected as the optimized formulation. The best fit model for optimized formulation was found to follow Korsmeyer-Peppas model.

INTRODUCTION

Oral submucous fibrosis (OSMF) has been mentioned in the Indian medical literature, since the time of Sushruta. Epidemiological studies show a unique prevalence of this premalignant condition in India and Southeast Asia. Though chewing betel quid is considered an important risk factor for OSMF, the exact etiology and pathogenesis is still obscure. Although, occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxta epithelial inflammatory reaction followed by a fibroelastic change in the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat". A thorough literature survey has been carried out on the effect of Cucurmin (Cu) on cytogenetic damage in patients suffering from OSMF. Curcumin a hydrophobic compound with very low water solubility is a natural polyphenol extracted from the plant *Curcuma longa*. It has a low aqueous solubility and poor bioavailability. The in-vivo studies indicate that orally administrated Cu under goes rapid metabolism in the liver, while when administered intraperitoneally or systemically undergoes reduction. Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and lipophilic central cavity. Hydrophilic drug cyclodextrin complexes are formed by inclusion of lipophilic drug or lipophilic drug moiety in the central cyclodextrin cavity. The literature survey reveals that no significant work has been reported in improving aqueous solubility and delivery of Cu by using HPβ-CD as Solid Lipid Nanoparticulate Jellies in treatment of OSMF. Therefore an attempt has been made to improve aqueous solubility and sustained the release of Cu with the aid of HPβCD inclusion complex and to design and evaluate for solid lipid nanaoparticulate jelly preparations using hydrophilic polymer like pectin.

MATERIAL AND METHOD

Material

Curcumin, Poloxomer 188 (surfactant), Pectin (Jelling agent) was purchased from Reasearch Lab., Fine Chem Industries, Mumbai. Dynasan 118 (Solid lipid), L-α- Phosphatidylcholine (Co-surfactant and lipid stabilizer) was purchased from Sigma Aldrich, Germany. Hydroxy Propyl β-Cyclodextrin was purchased from Hi-Media Laboratories Pvt. Ltd., Mumbai.

Method

Preformulation Studies

Organoleptic Characteristics

Curcumin, HPβCD and all the other excipients were evaluated for organoleptic properties such as colour, odour and appearance.

Micromeritic Properties

Bulk characterization of Curcumin and HPβCD was performed for bulk Density, Tapped Density, Hausner's Ratio, Angle of Repose and Compressibility Index.

Visual Solubility in various solvents:

The visual solubility of Cu was determined in the solvents such as distilled water (DW), Ethanol, Phosphate buffer 6.8, DW: Ethanol (9:1) and Phosphate buffer 6.8: Ethanol (9:1). Accurately weighed 10 mg of Cu were dissolved in 10 ml solvent and shaken for 1 hour on orbital linear shaker. The solutions were checked visually for their clarity.

Saturation Solubility Studies:

The saturated solubility of the Cu sample was determined in DW: Ethanol (9:1), by dissolving an accurately weighed 500 mg of Cu to 100 ml DW: Ethanol (9:1). The solutions were sonicated for 30 min for the attainment of equilibrium followed by filteration after 24 hrs of stirring and were analyzed at 426 nm on UV Visible Spectrophotometer (Jasco V-630). This procedure was repeated thrice for accuracy and precision.

Spectroscopic Studies

Determination of λ max of Curcumin in DW: Ethanol (9:1) and PBS pH 6.8: Ethanol (9:1) system

The UV absorption spectrum of a solution of Cu in DW and Ethanol (9:1) and Phosphate buffer 6.8 and Ethanol (9:1) were obtained using UV/VIS spectrophotometer (V-630, Jasco Corporation Tokyo, Japan) in 1 cm quartz cells. Accurately weighed 100 mg of Curcumin was dissolved in 100 ml of each solvent at room temperature to get the clear solutions that were subjected to UV scanning in 200 to 500 nm range on UV spectrophotometer. The λ max was observed.

Determination of Calibration Curve of Curcumin in DW: Ethanol (9:1) and PBS pH 6.8: Ethanol (9:1) system

Accurately weighed 100 mg of Cu was dissolved in 100 ml solvent system with DW: Ethanol (9:1) and PBS pH 6.8: Ethanol (9:1) to get stock solution I (SS I). The dilutions were prepared to get concentrations of 2, 4, 6, 8, and 10 µg/ml. Absorbance of each solution was measured in triplicate by taking DW: Ethanol (9:1) and PBS pH 6.8: Ethanol (9:1) as a reference standard.

Fourier Transform Infra Red (FTIR) Spectrophotometer

KBr was heated for 1.5 hr to remove moisture at 60° C. Cu was mixed thoroughly with KBr in proportion of 1:9. The FTIR spectrum from above mixture was measured under FTIR instrument by recording graph of % Transmittance vs. Wave No. (JASCO– FT/IR- 4100).

Differential Scanning Calorimetry (DSC) Study:

The DSC study of Cu was carried out using Mettler-Toledo DSC 823e equipped with an intercooler (Mettler-Toledo, Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample was hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min over a temperature range of 20-300°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

Analytical Method to confirm the presence of Curcumin

Thin layer Chromatography (TLC)

Thin layer chromatography was carried out to determine the presence of Curcumin sample obtained from Reasearch Lab., Fine Chem Industries, Mumbai.

a) **Developement of Mobile Phase:** Mobile Phase used was Toluene: Ethylacetate :Glacial acetic acid (9.2:0.5:0.3).

b) **TLC Analysis:**

1µg/ml solution of curcumin was prepared in methanol. TLC plates precoated silica gel aluminium plate 60 F254 with 250µm thickness; (E. MERCK, Darmstadt, Germany) of 10cm x 1cm and 10cm x 3cm were used. TLC plates were activated in oven at 60°C for 10 min prior to chromatography. Chamber saturation time with 10 ml mobile phase was 10 min at room temperature (30 ± 1° C) and RH (60 % ± 5). A spot of Cu methanol solution was applied at 2cm above from the end of the plate to be dipped in the mobile phase on individual activated plates of 10cm x 1cm. The plates were then carefully placed into the saturated chamber containing the

mobile phase and allowed to run till a particular distance on the plate. The plates were then carefully removed, air dried and observed visually.. The Rf values of these spots were calculated using the following equation:

$$Rf\ Value\ = \frac{\text{Distance compuond has moved from origin}}{\text{Distance of solvent front from origin}}$$

Drug and Excipients Compatibility Studies

Drug–excipients interaction was studied by FTIR spectroscopy. The spectra were recorded for pure Cu and excipients mixture using FTIR Spectrophotometer (Model No. FTIR4100 Jasco Corporation Tokyo, Japan).The scanning range was 400-4000cm^{-1} and the resolution of 1cm^{-1}.

Phase Solubility Study

The phase solubility study was carried out by the Higuchi and Connors method. The studies were performed in amber colored bottles to avoid any degradation of Cu and HPβ-CD. Different concentrations of HPβ-CD solutions such as 0, 2, 6, 8, and 10 µg/ml were prepared in DW: Ethanol (9:1) and filled in screw-capped amber colour bottles. Excess curcumin was added to these solutions to attain saturation. Each bottle was capped and shaken for 72 hrs in a constant temperature water bath at 30 ± 2°C. Following equilibrium, the solutions were filtered using 0.45-µm nylon disk filter, diluted, and assayed for the total dissolved Curcumin content by UV analysis (V-630, Jasco Corporation Tokyo, Japan). Each sample was determined in triplicate for accuracy and precision. The phase solubility diagram was constructed by plotting concentrations of dissolved Curcumin against CD concentration. The binding constant, K_s, was calculated from the slope of phase solubility plot.

$$\text{Ks} = \frac{\text{Slope}}{\text{S}_0\ (1 - \text{Slope})}$$

Where, S_0 is solubility of curcumin in the absence of HPβ-CD.

Where, S_0 are the solubility of drug in the presence and in the absence of CD, respectively.

Preparation of Inclusion Complex by Common Solvent Evaporation Method:

Appropriate quantities of Cu and HPβ-CD in ratio of (1:1) were dissolved in ethanol, was stirred for 24 h and then evaporated in order to remove ethanol completely. The preparation was allowed to evaporate and stirred by using magnetic stirrer at 30-35^{0}C temperature. The CD complex was pulverized and then sieve through # 80 sieve.

Characterization of Inclusion Complex:

The prepared inclusion complex evaluated as follow:

Percentage Yield:

The efficiency of the process is determined by the % yield. That was calculated using the following equation:

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Therotical Yield}} \times 100$$

Drug Content:

Accurately weighed Cu- HPβCD complex was dissolved in 10 ml of ethanol with continuous shaken for 1 hour on orbital linear shaker. Filtered the content and measured the absorbance on Double beam UV-Visible Spectrophotometer.

Solubility Studies of Cyclodextrin Complex:

Excess of Cu-HPβCD complex was dispersed in 25 ml of DW in screw-capped bottles and shaken continuously for 2 h at ambient temperature until equilibrium was attained. Supersaturated solution was filtered through a 0.22-µm nylon filter and further diluted with methanol and absorbance was measured at 426 nm.

Fourier Transform Infrared Spectroscopic (FTIR) studies:

Sample Cu and Cu-HPßCD complex were mixed with dry powdered potassium bromide and FTIR spectrum from above mixture was measured under FTIR instrument JASCO- FT/IR - 4100 by recording graph of % transmission Vs wave no.

DSC Studies:

Differential scanning calorimetric studies of Cu, and Cu-HPßCD complex were performed by using differential scanning calorimeter (DSC; Mettler Toledo Star system). Samples were weighed and placed in sealed aluminum pans. The coolant was liquid nitrogen. The samples were scanned at 10°C/min from 20°C to 300°C and thermograms were recorded.

Cumulative % Drug Release:

In vitro dissolution study was performed using the USP Type I (basket type) model. Accurately weighed complexes equivalent to 200 mg of Cu filled in a capsule of size 00 and were placed in the basket immersed in the dissolution vessels with 900 ml of PBS pH 6.8 37 ± 0.1°C and stirred at 50rpm. Samples were collected periodically and replaced with a fresh dissolution medium. A sample of 10 ml was withdrawn and filtered through Whatman filter paper and analyzed by UV-

visible spectrophotometer (Jasco, V630) Suitable dilutions were further made and absorbance read at 426 nm against blank.

Factorial Preparation of Solid Lipid Nanoparticles

Preparation of 2^2 Factorial Design

2^2 factorial batches of microparticulate dispersion were prepared by hot high shear homogenization method which consists of Dynasan 118 as lipid, Poloxomer 188 as surfactant and L-α- Phosphatidylcholine as co-surfactant in all the formulations, the amount of drug complex was kept constant. Accurately weighed Cu-HPβCD (1gm) was placed in beaker containing molten solid lipid at 75°C. Surfactant and co-surfactant were added subsequently, followed by making up the volume upto q.s.100 ml with double distilled water maintained at 75°C. The components were homogenized at 75°C using Ultra Turrex IKA T25, Remi Motors Ltd, RM-12C Mumbai at 3000 rpm for 30 mins to get microparticulate dispersion. The homogenous mixture was stored at refrigerated condition (2-8 ºC) until further use.

Evaluation of 2^2 factorial batches

Various parameters used for evaluation of the four batches B_1 to B_4, included visual observation for Phase separation on storage and Droplet size analysis, In-vitro cumulative % drug release and Encapsulation Efficiency (% EE).

Visual Observation

The prepared batches were observed visually for phase separation after 24 hr storage at 2-8°C and droplet size of the prepared dispersion was also determined by using Motic Digital Microscope.

% Entrapment Efficiency:

% EE was determined by centrifugation method. Accurately weighed amount was added to Eppendorf tube. The dispersion was then allowed to centrifuge at 1200 rpm for 40 min at 4°C in a cooling centrifuge (REMI, Mumbai, India) to separate the lipid and aqueous phase. 0.5 ml of supernatant was then diluted with ethanol to 10 ml and analyzed by UV-Vis spectrophotometer at 426 nm. The %EE was calculated by using the following equation:

$$\%\, EE = \frac{drug\ in\ suspension - drug\ in\ continuous\ phase}{drug\ in\ suspension}\ X\ 100$$

In vitro Cumulative Release of Cu from the dispersion:

A modified dialysis method was used to evaluate the *in vitro* release of dispersion. A dialysis bag (cellophane membrane, molecular weight cut off 10,000–12,000, Hi-Media, India) was soaked overnight in 100ml dissolution medium-PBS pH 6.8: Ethanol (7:3). To the pre-swollen dialysis bag, 2 ml of dispersion was placed and both the ends of bag were tied to prevent any leakage. Later, dialysis bags were carefully placed in the volumetric flasks containing the dissolution medium of 100 ml of PBS pH 6.8 –Ethanol system (7:3), which was stirred continuously at 100 rpm using Magnetic stirrer TH-100 Whirlmatic, Mega, 6 stations, Spectra lab, India. At selected time intervals, aliquots were withdrawn from the release medium and replaced with the same amount of dissolution medium. The sample was assayed spectrophotometrically for Cu at 426 nm.

Formulation of the Optimised Batch:

An optimized batch (SLN) was prepared using Dynasan 118 as lipid, Poloxomer 188 as surfactant and L-α- Phosphatidylcholine as the co-surfactant. Accurately weighed inclusion complex was placed in beaker containing molten solid lipid at 75^{o}C. Surfactant and co-surfactant were added subsequently, followed by making up the volume to q.s.100 ml with double distilled water, also maintained at 75^{o}C. The components were homogenized at 75^{o}C using Ultra Turrex homogenizer IKA T25, Remi Motors Ltd, RM-12C Mumbai at 3000 rpm for 30 mins to get microparticulate dispersion. This dispersion was subjected to ultrasonication using Probe Sonicator, PS 150, Orchid Scientifics and Innovatives India Pvt. Ltd. at 100% intensity for 90 mins. The formulation was passed through a 0.45µm Millipore filter and was stored at refrigerated condition (4ºC) until further use.

Evaluation of Optimised batch:

The prepared optimised batch evaluated for its appearance, % EE, in vitro % drug release and FTIR.

Formulation Development of Jelly

Method of preparation:

All the ingredients were weighed accurately, in one beaker pectin, propylene glycol, and citric acid were taken and heated to dissolved pectin and citric acid with constant stirring. In another beaker sugar syrup was prepared by adding 67 gm of sugar in a beaker and make up the volume

up to 100 ml. Sugar syrup was added to pectin solution and boiled for few minutes. Previously prepared and optimized SLN's containing Cu-HPβCD complex was weight accurately and added before jelly is allowed to set, mix thoroughly. These whole solutions was transferred in to moulds and then allow it for cooling and settling undisturbed by proper covering the moulds to avoid exposure to outer environment. After the jelly was set it is wrapped in to the gelatine paper and store in dry place.

Evaluation of Preliminary Trial Batches:

Appearance:

The prepared jelly was inspected visually for clarity, color and presence of any particulate materials.

Determination of pH:

The pH values of the prepared jellies were checked by using a calibrated digital pH meter (JENCO Vision Plus) at constant temperature. For the purpose 0.5 g of the weighed formulation was dispersed in 50 ml of distilled water and the pH was noted.

Swelling index:

Jelly were weighed individually (designated as w_1) and placed separately in petriplate containing phosphate buffer 6.8 pH. At regular intervals (30, 60, 90,120,150,180 min), samples were removed from the petriplate and excess water was removed carefully by using filter paper. The swollen jelly was reweighed (w_2). The swelling index of each system was calculated using the following formula.

$$\text{Swelling index} = \frac{W2 - W1}{W1 \times 100}$$

Spreadability:

The spreadability of formulations was determined. A jelly quantity 2.5 gm was placed between two slides and 1000 gm weight was placed over it for 5 min to press the sample to a uniform thickness. Weight 80 gm was added to pan. The time (in sec) required to separate the two slides were taken as a measure of spreadability. Sorter time interval to cover the distance of 7.5 cm indicates better spreadability. Spreadability was calculated by using the following formula.

$$S = M\frac{L}{T}$$

Where, S = Spreadability,

M= weight tide to upper slide

L = Length of glass slide (7.5 cm),

T = Time taken to separate two slides

Determination of Viscosity: (118-120)

A Brookfield cone and plate type Viscometer (CAP 2000+) was used to determine viscosity (cp) of the formulations. The viscosity was measured at 5 rpm after 30 seconds.

Content uniformity:

Jelly from each formulation were taken, crushed and mixed. From the mixture 10 mg of Cu equivalent of mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 426 nm. This experiment was repeated thrice and this average was chosen.

In-vitro dissolution studies:

The *In-vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP). The rotating paddle method was used to study the drug release from the jelly. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, at a rotation of speed of 100 rpm. 10 ml samples were withdrawn at predetermined time intervals and the volume was replaced with fresh medium. The samples were filtered through Whitman filter paper No.40 and analyzed for drug after appropriate dilution by UV spectrophotometer at 426 nm. The % drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8.

Formulation of Optimized Batch of jelly:

The effect of method variables on the responses were statically evaluated by applying one-way ANOVA at 0.05 level, using the commercially available software package Design-Expert version 8.0.7.1 in order to optimize the formulation parameters. On the basis of the results obtained optimized batch was formulated in the similar manner as the factorial batches with concentration of pectin and propylene glycol Optimized batch was evaluated for appearance, Determination of pH, Spreadability, Determination of Viscosity, Content uniformity and Invitro drug release.

Evaluation of Optimised Batch

Various parameters were used for evaluation for optimised batch which include appearance, Determination of pH, Spreadability, Determination of Viscosity, Content uniformity and Invitro drug release.

Appearance:

The prepared jelly was inspected visually for clarity, colour and presence of any particulate materials.

Determination of pH:

For the purpose 0.5 g of the weighed formulation was dispersed in 50 ml of distilled water and the pH was noted.

Spreadability:

The spreadability of a jelly quantity 2.5 gm was placed between two slides and 1000 gm weight was placed over it for 5 min to press the sample to a uniform thickness. Weight 80 gm was added to pan. The time (in sec) required to separate the two slides were taken as a measure of spreadability. Sorter time interval to cover the distance of 7.5 cm indicates better spreadability. Spreadability was calculated by using the following formula,

$$S = M\frac{L}{T}$$

Where,

S = Spreadability,

M= weight tide to upper slide

L = Length of glass slide (7.5 cm),

T = Time taken to separate two slides

Determination of Viscosity:

A Brookfield cone and plate type Viscometer (CAP 2000+) was used to determine viscosity (cp) of the formulations. The viscosity was measured at 5 rpm after 30 seconds.

Content uniformity:

Jelly was accurately weighed on an electronic balance and then transferred to 100 ml volumetric flask. Then, 90 ml of PBS 6.8 was added to dissolve the jelly. From that solution, pipet out 1 ml of the sample and diluted up to 5 ml with PBS 6.8. The amount of Cu present in each extract was determined using UV spectrophotometer at 426 nm. This procedure was repeated thrice for accuracy and precision.

***In-vitro* dissolution studies:**

The *In-vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP). The rotating paddle method was used to study the drug release from the jelly. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, at a rotation of speed of 100 rpm. 10 ml samples were withdrawn at predetermined time intervals and the volume was replaced with fresh medium. The samples were filtered through Whitman filter paper No.40 and analyzed for drug after appropriate dilution by UV spectrophotometer at 426 nm. The % drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8.

RESULT

The purpose of the present research has been focused to the latest developments related to innovative solid lipid carriers, in particular solid lipid nanoparticles (SLN) for oral delivery. SLN have evolved as lipid nanocarriers that exhibit the advantage of least toxicity, good stability, biocompatibility and easy to manufacture. In view of this, SLN of Cu-HPβCD were successfully formulated by employing hot high shear homogenization and ultrasonication technique in presence of the Dynasan 118 used as the solid lipid and Poloxomer 188 and L-α-Phosphatidyl cholineas surfactant and co-surfactant phase respectively.

The phase solubility study was carried out to optimize the ratio of Curcumin with HPβ-CD. Stable complex was formed with 1:1 ratio and stability constant (Ks) of 282.87 M^{-1} (Figure 1). FTIR studies reveal characteristics peaks of Cu-HPβCD in the complex (Figure 2). Saturation solubility of Cu had increased to (0.085mg/ml) that is 300 folds as compared to the pure Cu sample (0.00027mg/ml), indicating an improvement in saturation solubility after complexation with HPβ-CD.

FTIR studies shows Cu-HPβCD and excipients compatibility (Figure 5). The SLN successfully showed % EE of 83.46 ± 0.04 %. SEM results revealed spherical shape of Cu-HPβCD with a smooth surface (Figure 6).

In present research, an attempt was made to develop the formulation of Jelly of Curcumin HPβ-CD SLN's using different concentration of jellying agents such as pectin. Concentration of pectin was fixed on the basis of their consistency, effect on release pattern (Table VI). Batch P5 was selected on the basis of evaluation parameters such as drug content, pH, consistency,

viscosity, spreadability, swelling index and *In-vitro* Dissolution Studies (Table VII). Pectin and propylene glycol were selected as independent variables in the working concentration of 9 to 11 gm and 1 to 3 gm respectively on the basis of evaluation of batches. % Drug release was considered as a dependent variable. All factorial batches were evaluated for drug content, pH, consistency, viscosity and gel strength, *In-vitro* dissolution studies (Table VIII). The batch F2 showed 70.14% ± 0.25% drug release after 7 hour (Figure 8). Hence F2 was selected as the optimized formulation. The best fit model for optimized formulation F2 was found to follow Korsmeyer-Peppas model.

DISCUSSION

From the current study it can be discussed that the increase in solubility can attributed the HPβ-CD complexation and dispersed this complex of Cu-HPβCD in a form of SLN's, which improve the oral bioavailability in a sustained fashion of orally administrated jelly. The formulation of jelly is an easy to make, can be more organoleptically accepted particularly and by the pediatric patients. It would probably be one of best oral sustained release formulation useful in the treatment of OSMF.

REFERENCES

1. Taneja L, Nagpal A, Vohra P, Arya V. Oral submucous Fibrosis: An oral physician approach. Journal of Innovative Dentistry, Vol 1, Issue 3, Sept-December 2011.
2. Fareedi Mukram Ali, Prasant M.C, Ashok Patil, Vinit Aher, Safiya Tahsildar, Oral Submucous Fibrosis: Medical Management. GJMEDPH, Vol 1(1) Jan-Feb 2012,1-13.
3. M.K.Gupta, Shubhangi Mhaske, Raju Ragavendra, Imtiyaz. Oral submucous fibrosis-Current Concepts in Etiopathogenesis. People's Journal of Scientific Research,Vol 1 - July 08 39-40.
4. Salim Hosein, Amyn A. Malik. Oral Submucous Fibrosis: An Eastern Disease in the Western World. UTMJ Volume 88, Number 1, December 2010
5. Ajit Auluck, Miriam P. Rosin, Lewei Zhang, Sumanth KN.Oral Submucous Fibrosis, a Clinically Benign but Potentially Malignant Disease: Report of 3 Cases and Review of the Literature. JCDA , Vol. 74, No. 8 October 2008.
6. Shevale Vasant V,Kalra Rinku D, Shevale, Vruturaj V,Shringarpure Milind D. Management Of Oral Sub-Mucous Fibrosis : A Review. Indian Journal of Dental Sciences. Vol :4, Issue:2, June 2012.

7. Sunita N Dyavanagoudar. Oral Submucous Fibrosis: Review on Etiopathogenesis. Journal of Cancer Science & Therapy,Volume 1(2) : 072-077 (2009) – 072.
8. Tapasya Vaibhav Karemore, Vaibhav A Karemore. Etiopathogenesis and Treatment Strategies of Oral Submucous Fibrosis. Journal of Indian Academy of Oral Medicine and Radiology, October-December 2011;23(4):598-602.
9. Deepa Das A, Anita Balan, Sreelatha KT**.** Comparative Study of the Efficacy of Curcumin and Turmeric Oil as Chemopreventive Agents in Oral Submucous Fibrosis: A Clinical and Histopathological Evaluation. Journal of Indian Academy of Oral Medicine and Radiology, April-June 2010;22(2):88-92.
10. K. Purushotham. Rao, D. Vijaybhaskar,S. Pratima. Formulation of topical oral gel for the treatment of oral sub mucous fibrosis (OSMF). Scholars Research Library Der Pharmacia Lettre, 2011, 3(1): 103-112
11. Goel, A. Kunnumakkara, A. B., Aggarwal, B. B. (2008). Curcumin As"Curecumin": From Kitchen To Clinic. Biochemical Pharmacology 75, 787-809.
12. H. Hatcher, R. Planalp, J. Cho, F. M. Torti and S. V. Torti. Curcumin: From ancient medicine to current clinical trials. Cellular and Molecular Life Sciences. DOI 10.1007/s00018-008-7452-4 Birkhuser Verlag, Basel, 2008
13. Aggarwal, B. B., Sundaram, C., Malani, N., Ichikawa, H. (2007). Curcumin: the Indian solid gold. Advances in Experimental Medicine and Biology 595,1-75.

Tables

Table I: Organoleptic Properties of Curcumin and HPßCD

Sr. No.	Characterization		Observation	
			Curcumin	**HPßCD**
1.	Organoleptic properties	Colour	Bright Yellowish	White
		Odour	Characteristic	Odorless
		Taste	Slightly Bitter	Slightly Sweet
2.	Melting Point		180°C-185°C	

Table II: Micromeritic Properties of Curcumin and HPβCD

Sr. no.	Parameters	Observation Curcumin	Observation HPβCD
1	Bulk density (gm/ml) ±SD	0.52±0.03	0.571±0.01
2	Tapped density (gm/ml) ±SD	0.67±0.02	0.784±0.02
3	Hausner ratio	1.24	1.34
4	Compressibility index	19.42	27.12
5	Angle of repose	32±0.32	39.5±0.18

Table III: Visual Solubility of Curcumin in Different Solvent

Sr. No.	Solvent	Observation
1.	DW	Insoluble
2.	Ethanol	Soluble
3.	Methanol	Soluble
4.	Chloroform	Soluble
5.	DW: Ethanol (9:1)	Soluble
6.	PBS 6.8:Ethanol (9:1)	Soluble

Table IV: 2^2 Factorial Batches

Factorial Batch	Coded form		Actual form	
	P_1	P_2	% Lipid w/v	% Smix (S/Cos =3:1) % w/v
B_1	+1	-1	4.5	5.5
B_2	+1	+1	4.5	6.5
B_3	-1	+1	3.5	6.5
B_4	-1	-1	3.5	5.5

Table V: Evaluation of 2^2 Factorial Batches

Factorial Batch	Droplet Size (µm) after 24 hrs	Phase Separation after 24 hrs	% Entrapment Efficiency*	Cumulative % Drug Release*
B_1	1.2–2.4	No Phase Separation	82.26 ± 0.17	70.214 ± 0.03
B_2	1.2–2.4	No Phase Separation	82.38 ± 0.21	71.39 ± 0.01
B_3	1.2–2.4	No Phase Separation	81.15 ± 0.02	68.61 ± 0.031
B_4	1.2–2.4	No Phase Separation	80.12 ± 0.017	69.241 ± 0.017

Table VI: Formulation of Trial Batches

Ingredients (gm/100ml)	P1	P2	P3	P4	P5	P6	P7	P8	P9
Prepared SLN's of Curcumin	10	-	-	-	-	-	-	-	-
Pectin	1	2.5	5	7.5	10	12.5	15	17.5	20
Citric acid	1	-	-	-	-	-	-	-	-
Sugar Syrup	66.7	-	-	-	-	-	-	-	-
Propylene glycol	2	-	-	-	-	-	-	-	-
Sodium benzoate	0.01	-	-	-	-	-	-	-	-
DW	100	-	-	-	-	-	-	-	-

Table VII: Appearance, Consistency, pH, Average % Drug Content, Viscosity and Spreadability Time of the Formulations

Sr. No	Formulations	Appearance	Consistency	pH (±SD)	Average %drug content (±SD)	Viscosity (cp)	Spreadability Time(in sec) (±SD)
1	P1	Milky Yellow	Fluid	5.19 ±0.02	96.23 ±0.81	7581	15.50 ±0.45
2	P2	Milky Yellow	Fluid	5.13 ±0.01	98.01 ±0.36	8523	19.64 ±0.61
3	P3	Milky Yellow	Slightly Fluid	5.02 ±0.05	92.50 ±0.02	10324	28.41 ±0.72
4	P4	Milky Yellow	Acceptable	6.06 ±0.01	97.93 ±0.50	12171	36.31 ±0.31
5	P5	Milky Yellow	Acceptable	6.10 ±0.02	98.65 ±0.01	14689	46.12 ±0.85
6	P6	Milky Yellow	Acceptable	6.04 ±0.01	96.39 ±0.26	15960	48.34 ±0.85
7	P7	Milky Yellow	Slightly Thick	5.86 ±0.03	96.16 ±0.19	19666	49.96 ±0.61
8	P8	Milky Yellow	Thick	6.10 ±0.07	95.41 ±0.06	21369	53.51 ±0.25
9	P9	Milky Yellow	Thick	6.13 ±0.01	96.31 ±0.56	23141	59.81 ±0.89

Table VIII: Composition of Various Jelly Formulations Using Factorial Design

Ingredients (gm/100ml)	**Formulations**								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Curcumin-β CD Complex	10	10	10	10	10	10	10	10	10
Pectin	9	9	9	10	10	10	11	11	11
Citric acid	1	-	-	-	-	-	-	-	-
Sugar Syrup	66.7	-	-	-	-	-	-	-	-
Propylene glycol	1	2	3	1	2	3	1	2	3
Sodium benzoate	0.01	-	-	-	-	-	-	-	-
DW q.s. (ml)	100	100	100	100	100	100	100	100	100

Table IX: Appearance, Consistency, pH, Average % Drug Content, Viscosity and Spreadability Time of the Formulations

Sr. No	Formulations	Appearance	Consistency	pH (±SD)	Average %drug Content (±SD)	Viscosity (cp)	Spreadability Time(sec) (±SD)
1	F1	Milky Yellow	Slightly Fluid	5.21 ±0.007	98.04 ±0.04	15660	25.45 ±0.45
2	F2	Milky Yellow	Slightly Fluid	5.60 ±0.03	96.41 ±0.02	13766	32.67 ±0.61
3	F3	Milky Yellow	Slightly Fluid	5.11 ±0.01	98.20 ±0.05	13952	35.33 ±0.72
4	F4	Milky Yellow	Acceptable	5.23 ±0.007	96.29 ±0.04	14230	39.15 ±0.31
5	F5	Milky Yellow	Acceptable	5.65 ±0.02	95.48 ±0.09	14860	41.65 ±0.85
6	F6	Milky Yellow	Acceptable	5.79 ±0.02	98.24 ±0.02	15265	45.35 ±0.85
7	F7	Milky Yellow	Slightly Thick	5.08 ±0.007	97.30 ±0.02	15556	59.93 ±0.61
8	F8	Milky Yellow	Slightly Thick	5.09 ±0.007	96.22 ±0.02	16327	58.16 ±0.25
9	F9	Milky Yellow	Slightly Thick	6.05 ±0.07	98.11 ±0.03	16758	60.19 ±0.89

Figures

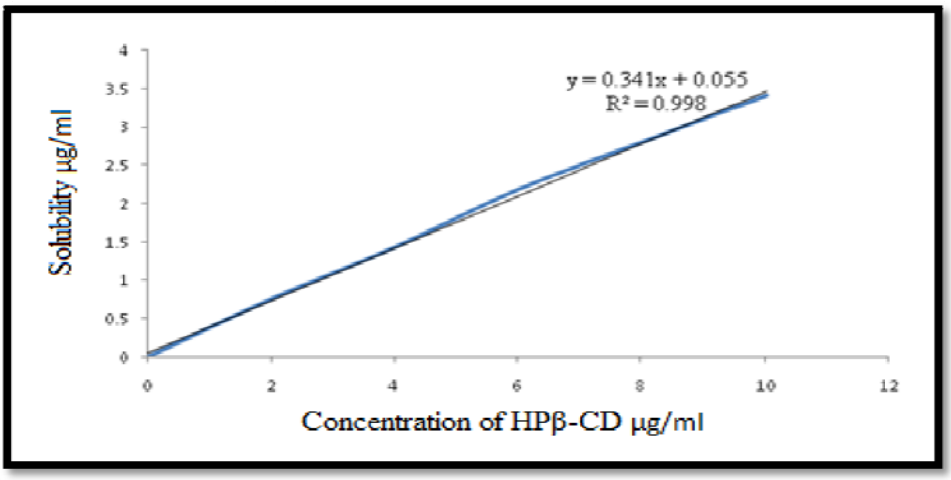

Figure 1: Phase Solubility Study of Cu with HPβ-CD

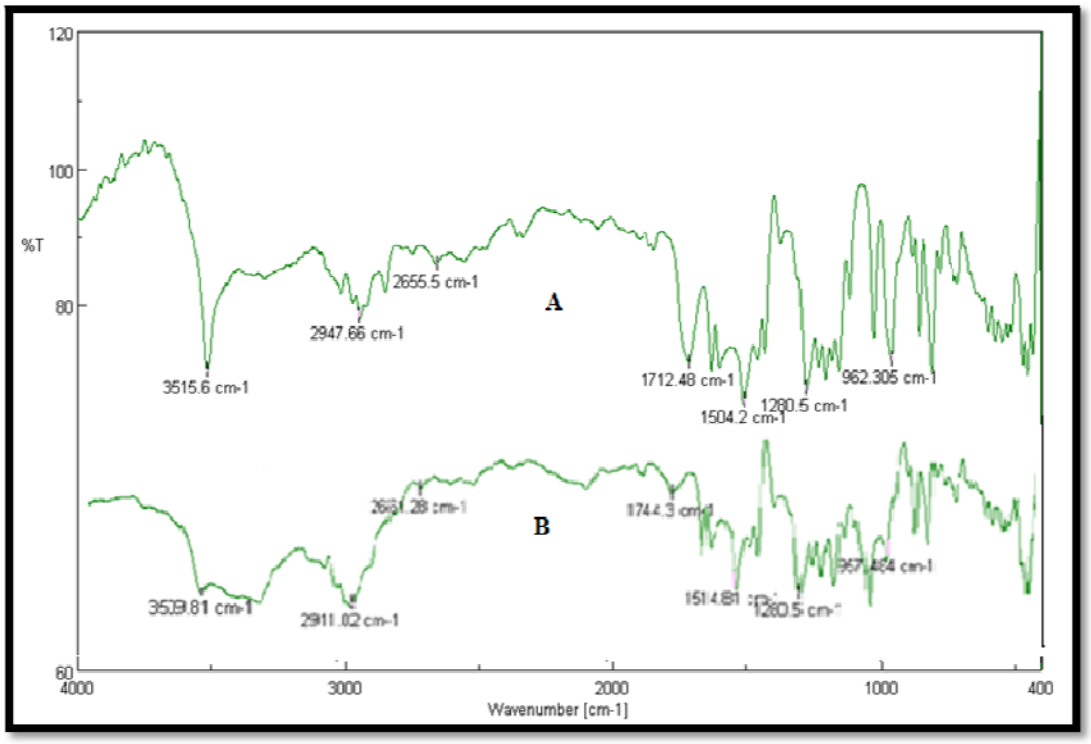

Figure 2: FTIR Spectra of: (A) Curcumin, (B) Curcumin + HPβ-CD complex

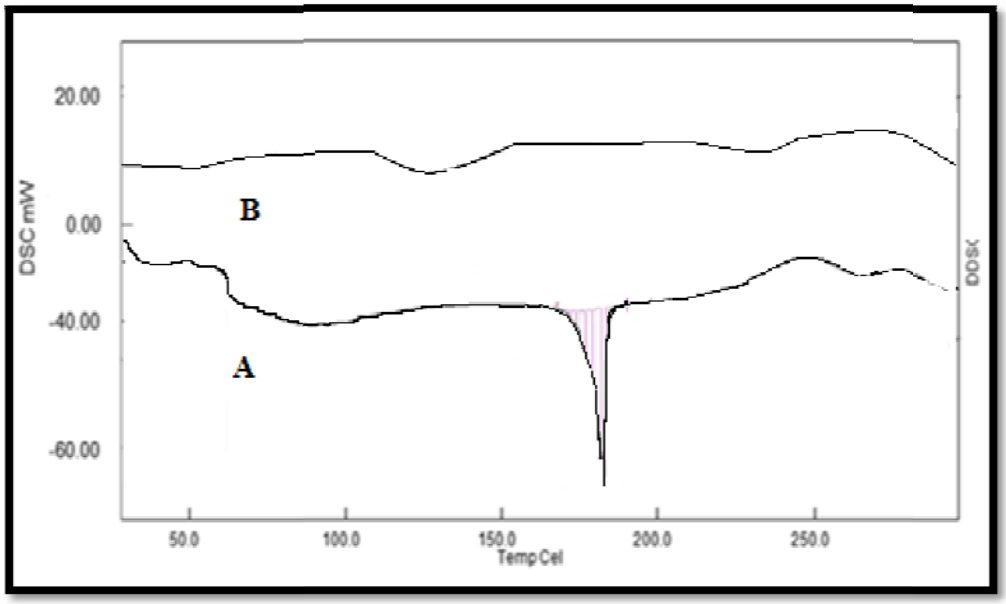

Figure 3: DSC Thermograms of (A) Pure Curcumin (B) Curcumin HPβ-CD Complex

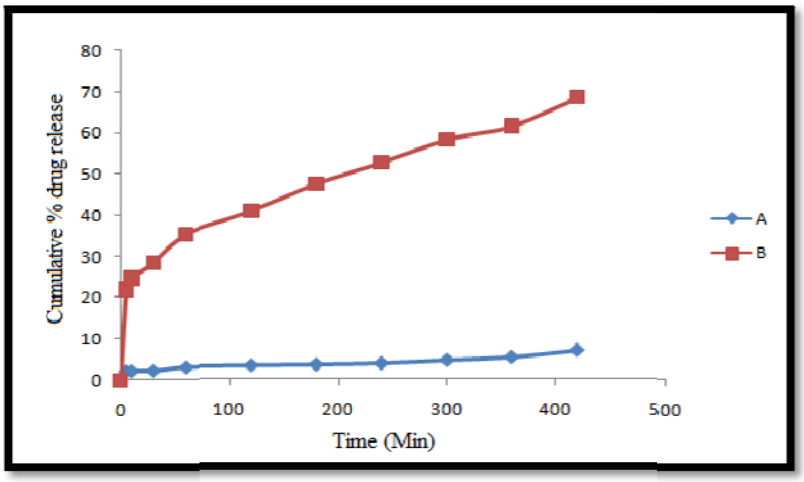

Figure 4: Cumulative % Drug Release of (A) Pure Curcumin and (B) Curcumin + HPβ-CD Complex

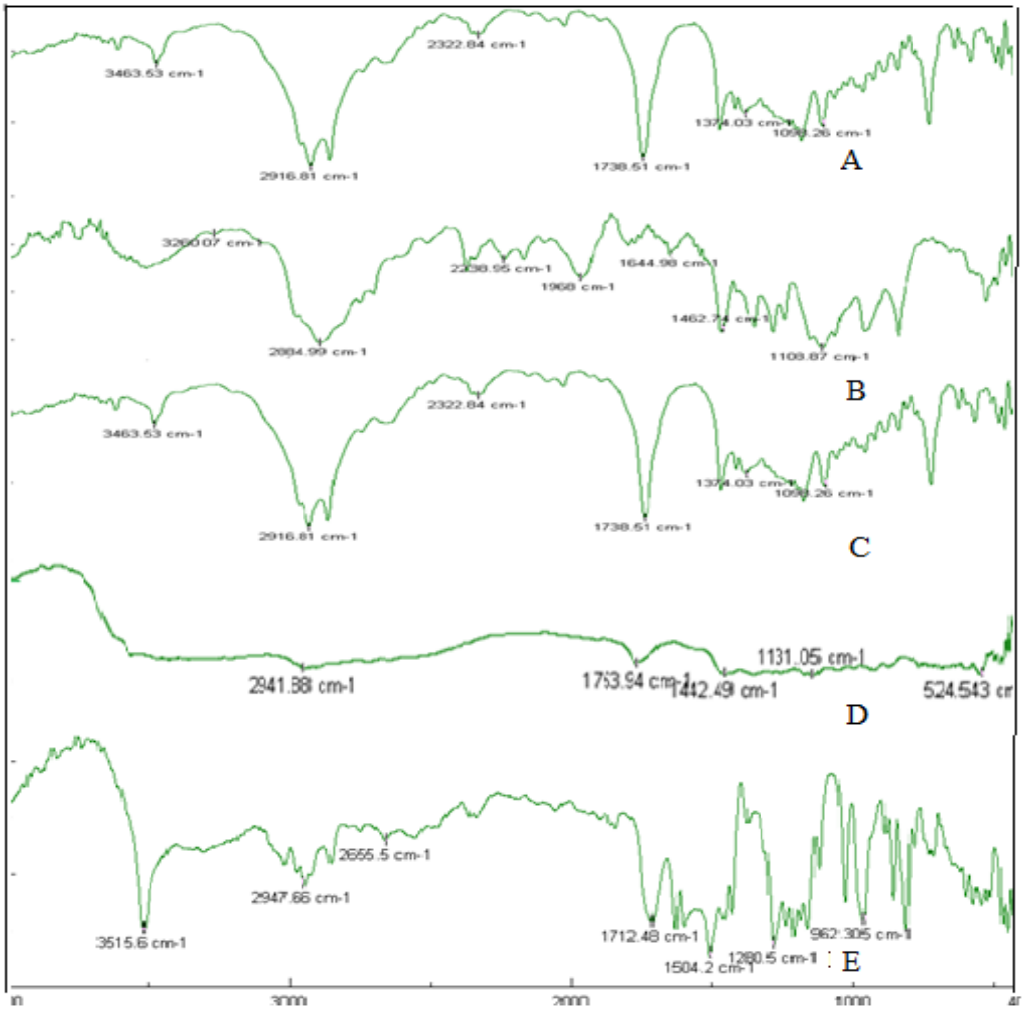

Figure 5: Drug-Excipients Compatibility Study(A= Cu+ Dynasan 188, B= Cu+ Polaxomer 188 , C= Cu+ L-α-Phosphatidylcholine ,D= Cu+ Pectin, E= Cu)

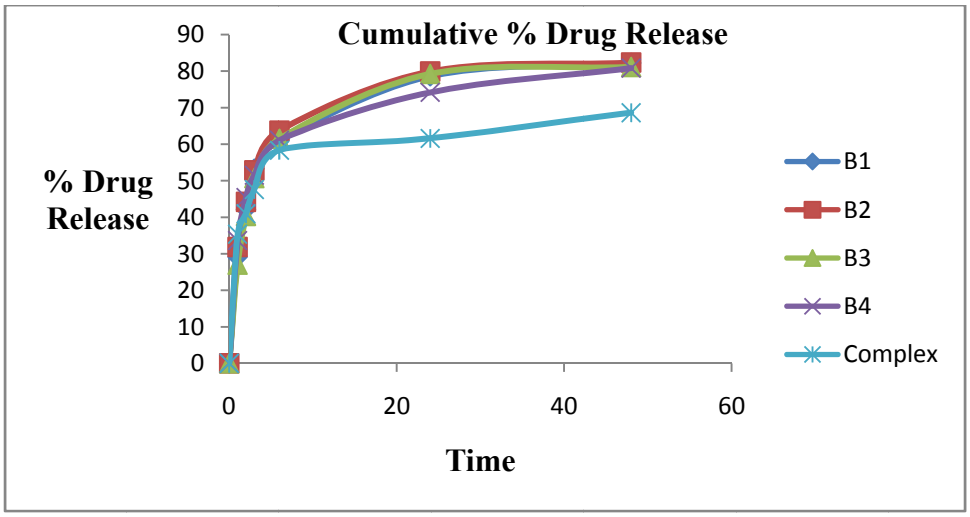

Figure 6: Cumulative % Drug Release of 2^2 Factorial Batches of SLN's B_1 to B_4 and Pure Drug Complex

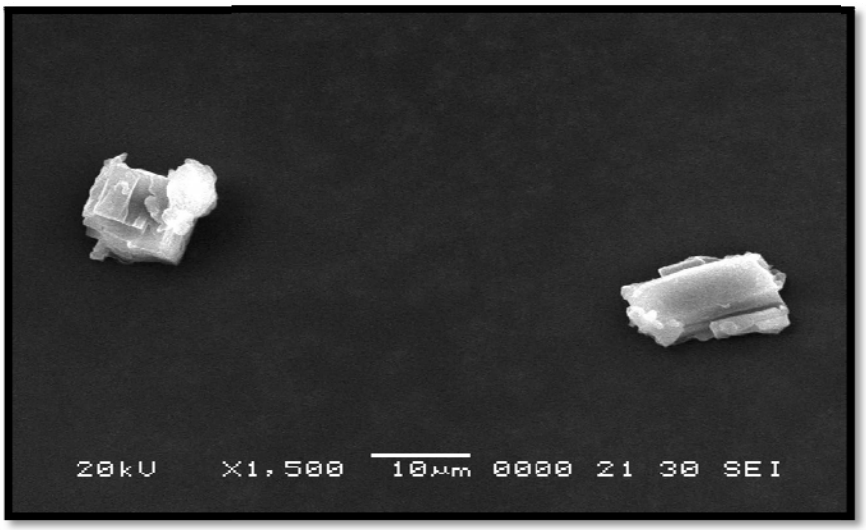

Figure 7: Scanning Electron Microscopy of SLN's

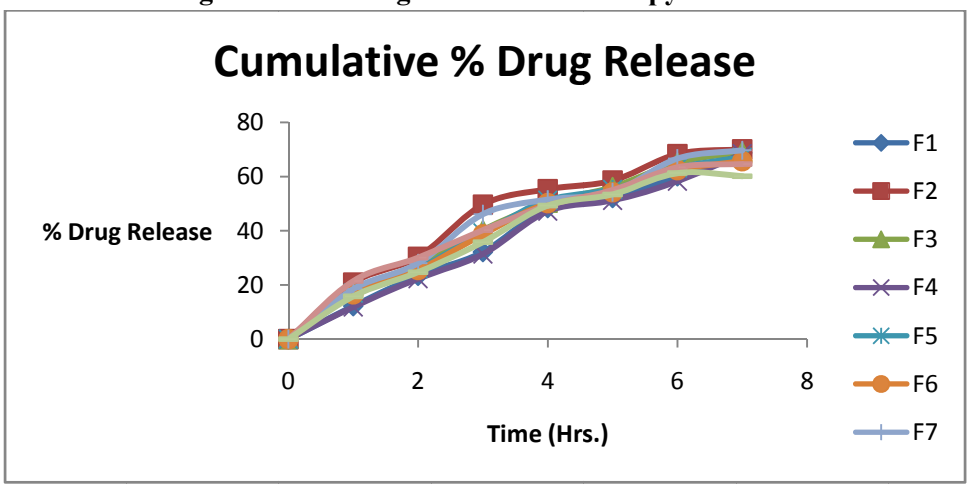

Figure 8: Dissolution Profile of Jelly containing inclusion complex of curcumin Batches F1 – F9

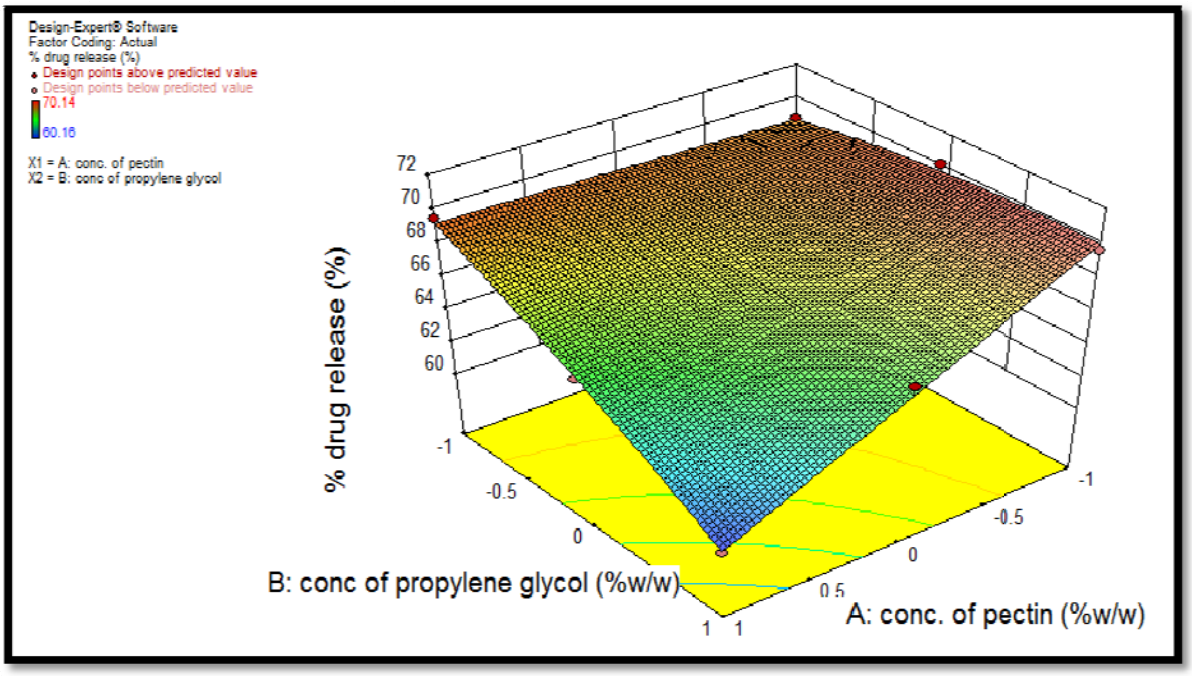

Figure 9: Response Surface Plot Showing Effect of Formulation Variables on Cumulative % Drug Release (Y)

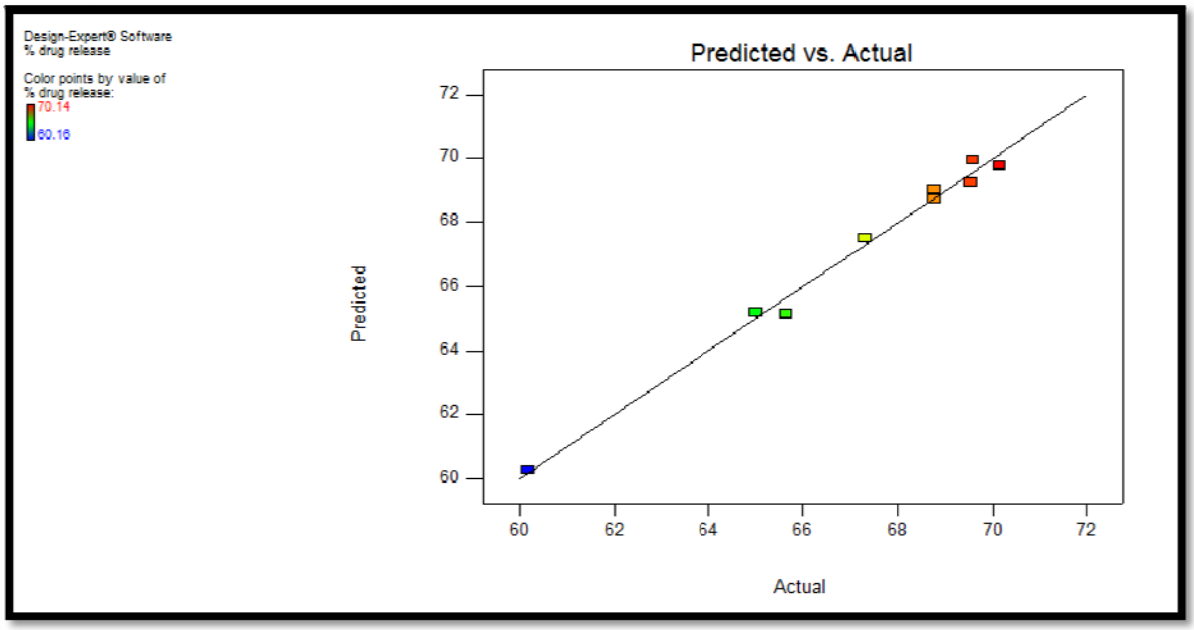

Figure 10: Correlation between Predicted and Actual Values For % Drug Release

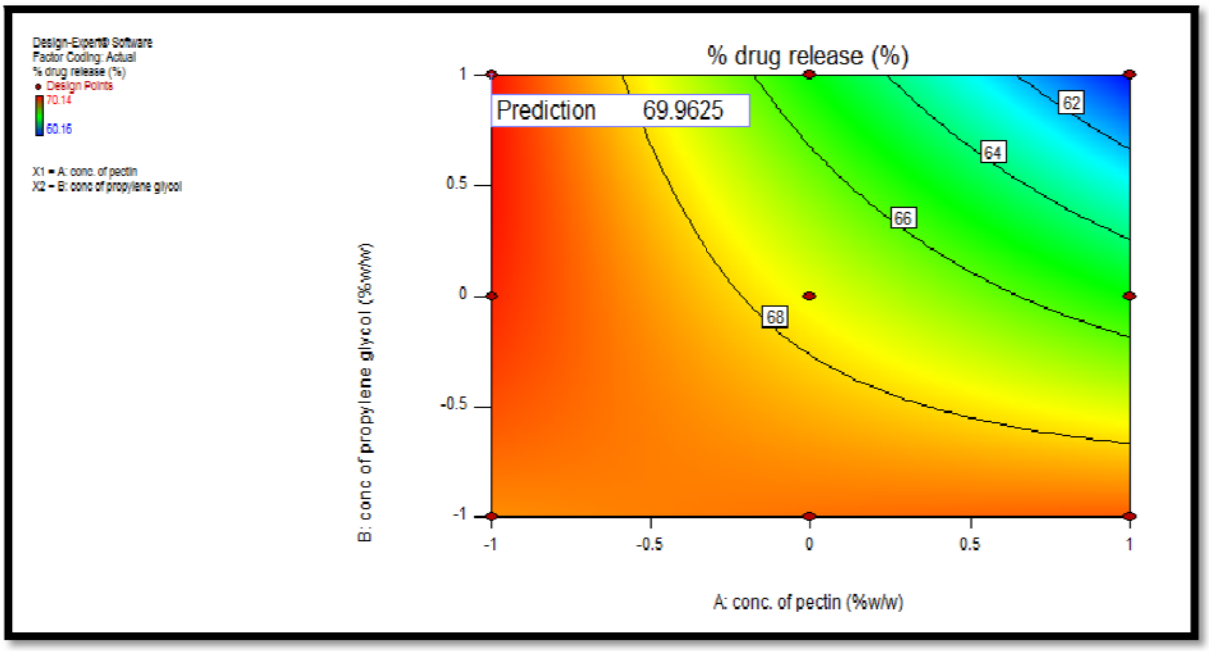

Figure 11: Contour Plot for % Drug Release