Design and Optimization of Aceclofenac Sustained Release Matrix Tablets Using 3^2 Factorial Design

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Abstract: Design, development and optimization of Aceclofenac SR matrix tablets by *direct compression technique. It is composed of two different ratios of waxes. The optimization was carried out by using 32 factorial designs with Design Expert Software. IR studies reveled that drug and the waxes are compatible with each other. The tablets were subjected for various evaluations like pre and post compression parameters. All the parameters are within the limits. The release profile showed that as the concentration of bees wax increases the drug release decreases and it was not steady after definite concentration of bees wax. This may due to poor binding between the drug and waxes. The formulation (F7) with the ratios of 0.31:0.15 bees and lanette waxes respectively Show best sustained release and flow property. The dissolution profile showed 58.74% at 8th hr. It was observed that the bees and lanette waxes fulfilled the conditions for an optimum formulation for sustain release.*

Keywords: Aceclofenac, matrix tablet, bees wax, lanette wax, design expert software, optimization

Introduction

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, aerosols and injectable. Even today these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems provide a timely release of drug. Therefore, to maintain the drug concentration in the therapeutically effective range, it is necessary to take several times a day. This result in a significant fluctuation in drug levels often with sub therapeutic and/or toxic levels and wastage of drug [1-4]. Recently several technical advancements have resulted in the development of new systems for controlling the rate of drug delivery, sustaining the extent of therapeutic activity the delivery of drug to the tissue.

The term "controlled release" implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and known mechanism of release. This means that the release of active ingredients from a drug inhibited release drug delivery system takings at a rate that is not only expected kinetically, but also reproducible from one unit to other. On the other hand the "sustained release" is usually used to explain a pharmaceutical dosage form prepared such that the liberation of the drug in the systemic circulation is prolonged over time resulting in plasma profile, which is sustained in duration [5-9].

The aim of most of the original controlled release systems was to attain a delivery profile that would produce a high blood level of the drug over an extended period of time in which the level raises after each administration of drug and then reduces until the next management. The key point with traditional drug administration is that the blood level of the agent should stay behind between a highest value, which may represent a lethal level, and a minimum value, lower than which the drug is no longer effective. In controlled drug delivery system designed for long term application, the drug level in the blood follows the profile as exposed in fig, lasting constant, between the required maximum and minimum, for prolonged period of time.

Drugs can be administered through different routes; however of all the routes of administration, oral rote of administration is most convenient for administering drugs for systemic effect because of ease of administration by manufacturing and dosage adjustments. Oral route of drug administration has wide acceptable and of the drugs administered orally in solid dosage forms represents the preferred class of product[6]. Solid dosage form of tablets and capsules are more commonly employed, the tablets have advantages than capsules in that they are tamper resistant and any adulterant of the tablet after its manufacture is almost certain to be observed.

Ideal candidate for sustained release or controlled release drug delivery system:

The desired biopharmaceutical characteristics of drug to be used in the development of per oral controlled release dosage forms are:

1. **Molecular weight:** <1000 daltons
2. **Solubility:** 0.1mcg/ml
3. **Pka:** >0.1% to 1% at pH 1 to 7.8
4. **Apparent partition coefficient:** o.5 to 2.0
5. **General absorbability:** from all GI segments
6. **Stability:** stable in GI environment. Released should not be influenced by Ph and enzyme.
7. **Less protein binding:** To evaluate whether a drug is viable candidate or not for the design of per oral controlled release formulation, one must consider the following pharmacokinetic parameters of the drug.
8. **Elimination half-life:** Preferably between 0.5 and 8 hrs.
9. **Total body clearance:** Should not be dose dependent.
10. **Elimination rate constant :** required for the design
11. **Absolute bioavailability:** should be 75% or more
12. **Absorption rate:** must be greater than release rate
13. **Therapeutic concentration:** the lower c_{ss} and the smaller v_d the lesser is the amount required.
14. **Apparent volume of distribution (V_d):** the larger the v_d MEC the larger will be the dose size required. The maximum dose to be incorporated in to a per oral control release formulations is about 500mg. The smaller the v_d, the easier is incorporation of drug into dosage form.
15. **Minimum toxic concentration (MTC):** MTC and MEC, the further apart this values are, the safer the dosage and also suitable for drugs with very short half-life.

Optimization Techniques

It is defined as follows: choosing the best element from some set of available alternatives.

- In pharmacy the word “optimization” is found in the literature referring to any study of formula.
- In development projects pharmacist generally experiments by a series of logical steps, carefully controlling the variables and changing one at a time until satisfactory results are obtained. This is how the optimization done in the pharmaceutical industry.
- Optimization is an act, process, or methodology of making design, system or desition as fully perfect, functional or as effective as possible.
- Optimization of a product or process is the determination of the experimental conditions resulting in its optimal performance.

Experimental Design

A full factorial 3^2 designs were used for optimization procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second order polynomial

model, thus enabling optimization of the time-lagged coating process. Mathematical modeling, evaluation of the ability to fit to the model, and response surface modeling were performed with employing Design-Expert. A 3^2 randomized reduced factorial design was used in this study and 2 factors were evaluated, each at 3 levels; experimental trials were performed at all 9 possible combinations prepared. The percentage of Bees wax (X_1) and Lanette wax (X_2) were selected as independent variables. Drug released, and Hardness was selected as dependent variables. The batches thus prepared by factorial design are evaluated and the effect of individual variable is studied according to the response surface methodology.

$$Y = b_0 + P_1X_1 + P_2X_2 + P_{12}X_1X_2 + P_{11}X_{21} + P_{22}X_{22}$$

where Y is the dependent variable, b 0 is the arithmetic mean response of the 9 runs, and bi (P_1, P_2, P_{12}, P_{11}, and P_{22}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2,X_1X_2, X_{12}, and X_{22}), which represents the average result of changing 1 factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_{21} and X_{22}) are included to investigate nonlinearity.

Methodology

Determination of λ_{max} of Aceclofenac

Absorption spectra of Aceclofenac

a) A solution of 1µg/ml Aceclofenac prepared by dissolving 100mg of a drug in 5 ml of methonal and make up to 100 ml with phosphate buffer pH 6.8 in a volumetric flask.
b) Then the solution was diluted and the λ_{max} of solution found in the range from 200-400 nm.
c) The absorbtion maxium was found to be 274nm.

Determination of Standard curve of Aceclofenac

a) Weigh accurately 1mg of Aceclofenac and dissolve in 5 ml of methonal and made up to 100 ml with phosphate buffer pH 6.8 in a standard flask to get 10µg/ml solution.
b) Then the solution was serially diluted to get 5, 10, 15, 20, 25 and 30 µg/ml stock solution and the λ_{max} of the stock was found out.
c) The absorbance of the diluted solutions was measured in a UV spectrophotometer at 274nm.
d) A calibration curve was plotted by taking concentration of the solution in µg on X-axis and absorbance on Y-axis and correlation co-efficient "r" was calculated.

Preparation of Sustained Release Matrix Tablet

The ingredients (listed in table no.5) were accurately weighed and sifted through sieve #60, magnesium stearate and talc sifted through sieve #80. Then the materials blended except magnesium stearate and talc for 20 minutes in ascending order. Then the powder mixture blended with magnesium stearate and talc for 5 minutes.

Evaluation of Powder Blend

Bulk Density

The powder blend under test was screened through sieve no 18. And 10g was \accurately weighed and filled in a 25ml graduated cylinder and the powder was levelled and the unsettled volume, V_0 was noted.

Bulk density (δ_0) = M/ V_0

M = Mass of powder taken

V_0 = Apparent unstrried volume

Tapped Density

The powder blend under test was screened through sieve no.18 and the weight of sample equivalent to 10g was filled in 25ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_0 was noted. Tapping was preceded further for an additional tapping 750 times and tapped volume, V_b was noted. The tapping was continued until difference between two successive tapped volumes was less than 2%. The tapped density was calculated in g/cm^3 by the formula.

Tapped Density (δ_t) = M/V_f

M = Weight of sample powder

V_f = Tapped volume

Carr's index

The carr's index of the powder was determined by using:

Carr's index (%) = [(TBD - LBD) × 100]/TBD

LBD = Loose bulk density

TBD = Tapped bulk density

Hausner ratio

Hausner ratio is calculated from the formula:

Hausner ratio= ($\delta t/ \delta_0$)

δt = Tapped density

δ_0 = Bulk density

Angle of repose

It is determined by the funnel method. 10g of the powder was accurately weighed and taken in a funnel and closed at the bottom with a cotton plug. Height of the funnel was adjusted such that the tip of the funnel touches the heap of the powder. The powder was allowed to flow through tunnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\textbf{Tan } \theta = h/r$$

Therefore,

$\theta = \tan^{-1} h/r$

θ = angle of repose

h = height of the cone

r = radius of the cone base

Evaluation of Tablets

Weight variation

Weight variation test for the tablets was performed as per the IP procedure. Ten tablets were weighed individually and the average weight was determined. The individual weights of all the ten tablets were noted. The percentage deviation of the individual weights from the average weight was then calculated. Deviation was not exceeding the values given in the table:

Tablet thickness: The thicknesses of the tablets were determined by using vernier calipers, and the results are expressed as mean values of 10 determinations.

Tablet hardness: Tablet hardness has been defined as the force required for breaking a tablet in a diametric compression test. A tablet was placed between two anvils of the hardness tester, force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded.

Drug content

Ten tablets were randomly sampled from each formulation batch, finely powdered and individually estimated for the drug content after suitable dilution, using UV-VIS spectrophotometer (UV-1601, Shimadzu) at 313.5 nm.

Friability test

The friability of the tablets was measured in a friability apparatus (Camp-bell Electronics, Mumbai). Ten tablets were initially weighed (w_{intial}) and placed in the friabilator. The friabilator was operated at 25rpm for 4 minutes and then the tablets were dedusted and weighed final (w_{final}). Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%. Determintion was made in triplicate.

$$\%\, friability = \frac{\text{Wintial} - \text{Wfinal}}{\text{Winitial}} \times 100$$

Disintegration test

Disintegration test was done by using disintegration appratus (camp-bell electronics, Mumbai). Place one tablet in each of the 6 tubes of the basket Disintegration apparatus was used without disc. The apparatus using distilled water was maintained at 37±2ºC. The assembley should be raised and lowered between 28-32 cycles per minute in the solution maintained at 37±2ºC. The time taken for complete disintegration tablet with no palpable mass remaining in the apparatus was measured and recorded.

***invitro* drug release studies**

The *in vitro* release of the drug of all formulations were performed using USP apparatus Type I (Basket) Electro lab, India. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. Dissolution was performed at 37±0.5°C, with stirring speed of 100 rpm. 5 ml of solution was withdrawn at time intervals of 5min,15min,30min,1,2,3,4,5,6,7,8 Hrs. The medium was replaced with same amount of fresh dissolution media each time. The then solutions were make upto 10 ml with the dissolution media. The samples were analyzed by UV-VIS spectrophotometer (UV-1700, Pharmaspec, Shimadzu Ltd, Japan) at 274nm and absorbance were recorded.

Stability Studies

Stability testing of tablets were carried at accelerated conditions at extreme temperature of 40^0C RH of 70 %±5%C.The sample were withdrawn at 30^{th} and 45^{th} days and evaluated for physical appearance, drug content ,hardness and dissolution studies the data was given the table .The results obtained at those temperatures has no effect on hardness, physical appearance, dissolution time.

Results and Discussion

Drug-Polymer Interaction/Compatibility Study Using FTIR

The IR spectra of drug and the excipients are shown in the figure from the ir spectra it was observed that there was no major changes in the peak positions of drug and mixture drug with recipients, it showed that there was no interactions between drug and excipients

Spectrophotometric characterization

Determination of λmax of Aceclofenac

A solution of 1µg/ml Aceclofenac prepared by dissolving 100mg of a drug in 5 ml of methonal and make up to 100 ml with phosphate buffer pH 6.8 in a volumetric flask. Then the solution was diluted and the λ_{max} of solution found in the range from 200-400 nm. The absorbtion maxium was found to be 274nm.

Standard calibration curves of Aceclofenac

Calibration curve of aceclofenac sodium was constructed in 5% of methanol and phosphate buffer with pH 6.8 at 274 nm using uv spectrophotometer. The calibration curve shows linearity in the range of 5-30Calibration curve of aceclofenac sodium was constructed in 5% of methanol and phosphate buffer with pH 6.8 at 274 nm using uv spectrophotometer. The calibration curve shows linearity in the range of 5-30µg/ml and regression coefficient value of 0.995.

Pre compression parameters

All the materials are passed through mesh 60# as per the composition shown in the table 4. They were evaluated for the pre-compression studies shown in the table 4 .The bulk density and the tapped density are in the range of 0.51gm/cm^2 -0.56gm/cm^2 and 0.58gm/cm^2-0.75gm/cm^2 respectively. The carr's index and Hausners ratio were found to be 13.29%-26.31%, 1.15-1.35 respectively and angle of repose was found to be 26.56-32.61.All formulations shows good to fair flow property. The F7 formulation showed better physical properties than the other formulations shown in the below table.

Post compression parameters

The tablets are prepared by direct compression method as per the table 5. The prepared formulations were evaluated for weight variation, hardness, friability they were shown in the table. The percentage weight variation found to be in the limit of ± 5%, hardness was in the range of 3-5 kg/cm^3 indicating that all the formulations showed good mechanical strength and the friability was in the limit of < 1% as per B.P.

***In vitro* dissolution studies**

The dissolution studies were carried out for the formulations as per the British Pharmacopoeia. The release data of all the formulations are shown in the table, and they are

diagrammatically represented in the figure 6. From the table it shows that the formulation with Bees and Lanette waxes in the ratio of 0.15:0.31 showed sustained release of drug. It was observed that as the concentration of Bees wax increases the rate of drug release was retarded and it was not steady after definite concentrations of Bees wax. The reason for this is may be due to Bees wax has a retardant property and poor binging between the drug and the waxs.

Drug release kinetics

In-vitro release data obtained for the optimized formulation was subjected to kinetic analysis. The percentage cumulative release were fitted into zero, first, Higuchi's, Korsmeyers-peppas equation to understand the mechanism of drug release from the Aceclofenac optimized formulation as shown in the figure 7,8,9,10. The regression coefficient indicates that the best formulation fits with Higuchi's kinetics and the slope showe that it followed non fickian mechanism of drug release.

3^2 Full Factorial Designs

in-vitro Drug Release of Matrix tablet according to the 3^2 Full Factorial Design (F1–F9). From Figure 5, 6 it was observed that 70mg of Bees and Lanette waxes in F7 formulation shown release of 58.74 at 8^{th} hr and showed Hardness of 3.3 kg/cm^3.

Dissolution Studies

In the formulations from F1 to F9 dissolution time was in the range of 58.74 – 75.41 ±1.23 %. Among all the formulations optimum dissolution was in the range of 58.74 ± 1.23 %. Both the waxes (bees and lanette waxes) showed significant effect on dissolution as the con centration of the lanette wax increases the release of drug decreased.

The effect of the variables on the Dissolution time profile in the optimized formulation F7 shown in following equation.

$$Y= - 134.02–2.859X_1–2.858X_2$$

Hardness

In the formulations from F1 to F9 dissolution time was in the range of 3.3 – 3.9 ±1.47 kg/cm^3. Among all the formulations optimum hardness was in the range of 3.3 ± 1.47 kg/cm^3. Both the waxes (bees and lanette waxes) showed significant effect on hardness as the con centration of the lanette wax increases the hardness also decreased.

The effect of the variables on the Hardness in the optimized formulation F7 shown in following equation.

$$Y= 57.619+0.77X_1+0.769X_2$$

Stability studies of optimized formulation

Stability testing of tablets were carried at accelerated conditions at extreme temperature of 40^0C RH of 70%±5%.The sample were withdrawn at 30^{th} and 45^{th} days and evaluated for physical appearance, drug content and dissolution studies .The results obtained at those temperatures has no effect on physical appearance, drug content dissolution time.

Conclusion

Aceclofenac sustained release tablets were formulated by using Bees wax and Lanette wax. Infrared spectra of the drug reveal that there is no significant interaction between drug and waxes. Preformulation studies were done initially and the results were found within the

limits. The evaluation tests results are found to be within pharmacopoeial specifications. From *in-vitro* dissolution study it is concluded that the formulation of sustained release tablet of Aceclofenac containing Bees wax and lanette waxes in 70 mg proportions were taken for optimizing formulation of sustained release tablet for 8 hours release as it fulfills all the requirement of sustained release tablet. Kinetic studies were observed as Non-fickian release mechanism of drug through waxes. From the stability studies, it was concluded that no significant difference in the drug content between initial and formulations stored at 40C ±2^{0}C, for 45 days at RH 70±5% for 45 days in optimized formulation F7.

Table 1: Composition table of matrix Aceclofenac tablet

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Aceclofenac sodium(mg)	150	150	150	150	150	150	150	150	150
Lanette Wax(mg)	51.25	47.50	45.25	40.75	29.25	25.75	22.5	18.75	15.25
Bees Wax(mg)	18.75	22.5	25.75	29.25	40.75	45.25	47.50	51.25	54.75
Lactose(mg)	25	25	25	25	25	25	25	25	25
Talc(mg)	5	5	5	5	5	5	5	5	5

Table 2: calibration curve data for aceclofenac

Concentration(µg)	**Absorbance(nm)**
5	0.276
10	0.365
15	0.517
20	0.621
25	0.765
30	0.912

Table 3: FTIR spectral analysis

Functional Group	**Characteristic Peaks (Cm-1)**	**Observed Peaks (Cm-1)**
2^0 NH	3318	3216
C=O	1771	1056
Ar-C-Cl Stretching	1056	1716
Di Substitutional Aromatic Ring	609	608

Table 4: pre-compression Parameters of Aceclofenac sustained release tablets

Formulation Code	Bulk density (gm/cm²)	Tapped density (gm/cm²)	%Carr's index	Hausner's ratio	Angle of repose
F1	0.52	0.65	20	1.25	27.47
F2	0.544	0.7	22.22	1.28	28.81
F3	0.526	0.66	21.05	1.26	32.61
F4	0.54	0.67	20	1.25	32.61
F5	0.562	0.75	25	1.33	29.68
F6	0.533	0.68	22.22	1.28	32
F7	0.510	0.74	26.31	1.35	30.11
F8	0.547	0.74	26.31	1.35	30.11
F9	0.515	0.65	21.05	1.26	32.61

Table 5: Post-compression Parameters of sustained release tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm³)	Friability %	Thickness (mm)	Disintegration time (mins)	Drug content %
F1	251±2.31	3.9± 0.16	0.67	5.6	33	82
F2	248±2.13	3.7± 0.14	0.71	5.3	35	86.66
F3	252±2.48	4.2± 0.21	0.53	6.2	37	88.66
F4	249±2.87	3.3± 0.09	0.42	5.4	39	80
F5	251±2.23	3.6± 0.12	0.32	5.6	41	94.66
F6	247±1.98	3.8± 0.14	0.45	5.8	43	92
F7	248±2.02	4.4± 0.08	0.21	6.4	45	97.33
F8	253±2.23	3.5± 0.11	0.39	5.3	36	92.66
F9	252±2.10	3.7± 0.21	0.53	5.4	33	90.66

Table 6: *In-vitro* dissolution studies for matrix tablet

TIME (HRS)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
5 min	3.84	2.76	0.96	0.84	0.6	9.31	10.51	9.31	2.64
15min	17.40	18.72	18.36	18.24	17.64	16.57	11.74	16.57	18.48
30min	20.05	21.38	21.98	23.42	22.69	21.13	21.13	21.13	21.14
1	27.74	29.42	30.38	30.38	26.78	30.26	25.46	30.26	25.58
2	31.71	33.15	34.35	33.87	33.26	32.07	32.06	32.07	29.54
3	42.27	38.91	43.59	45.39	33.87	35.55	35.55	35.55	39.03
4	44.08	45.40	45.40	47.09	42.87	38.91	38.91	38.91	45.16
5	50.56	53.69	54.29	54.29	46.00	46.48	46.48	46.48	49.49
6	53.45	56.33	56.10	56.70	50.57	48.77	48.77	48.77	54.53
7	58.01	57.90	53.22	59.10	59.93	54.41	54.41	54.41	52.62
8	73.98	69.90	68.81	65.10	63.66	72.18	58.74	68.58	75.41

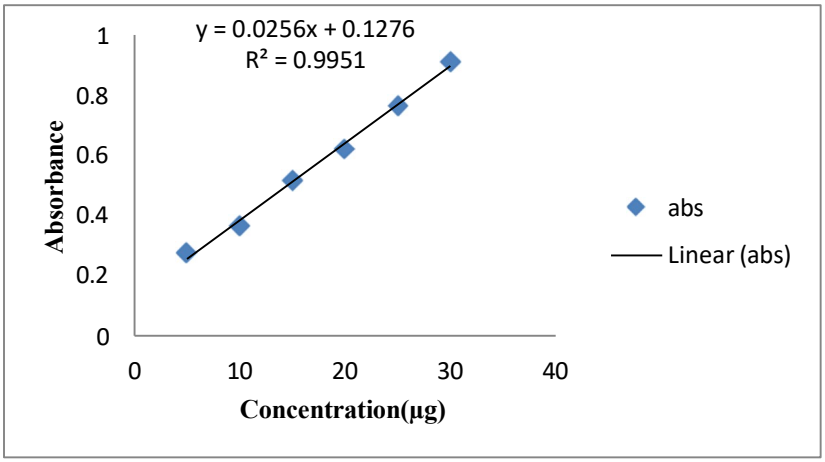

Figure 1: calibration curve of aceclofenac in 6.8 phosphate buffer at 274nm

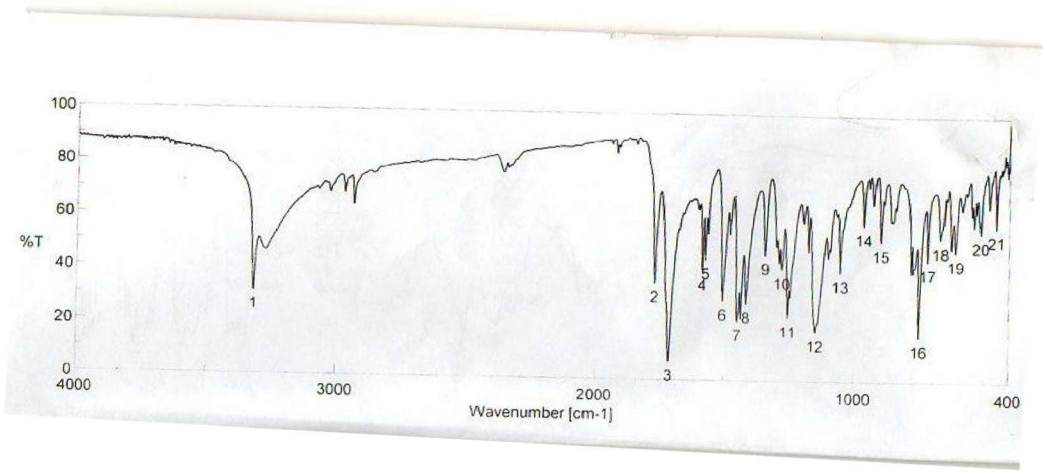

Figure 2: FTIR Spectral analysis of Aceclofenac Sodium

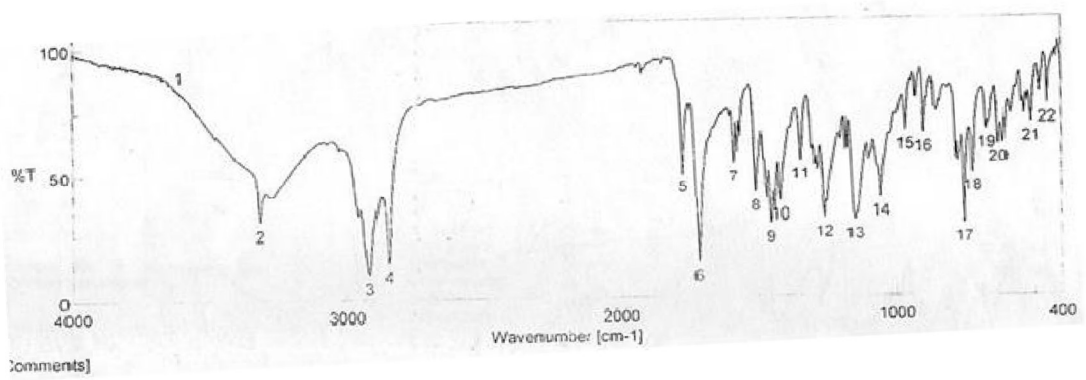

Figure 3: FTIR spectral analysis of physical mixture of Drug and Bees and Lanette waxes

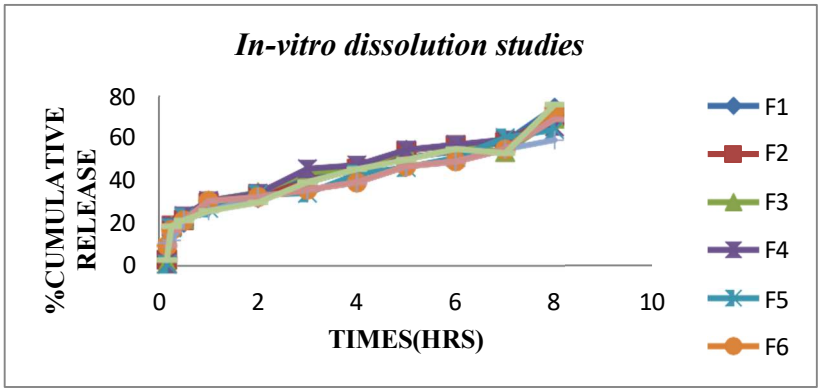

Figure 4: *In-vitro* dissolution studies for different formulation

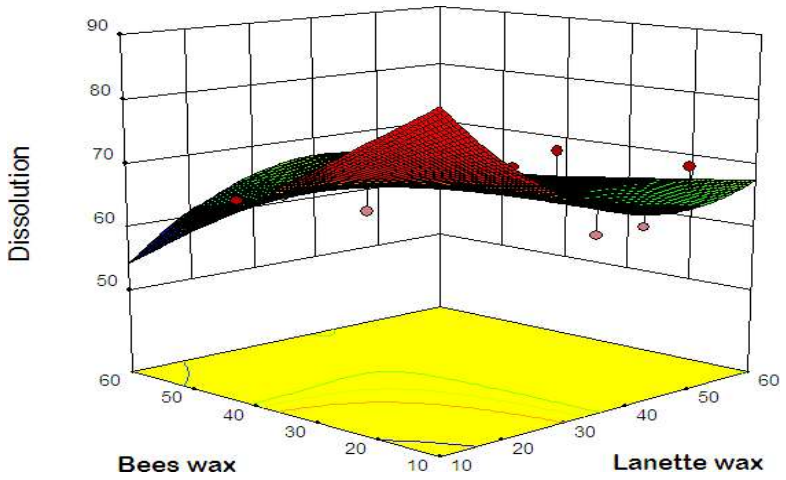

Figure 5: Response surface plot showing the influence on dissolution time profile

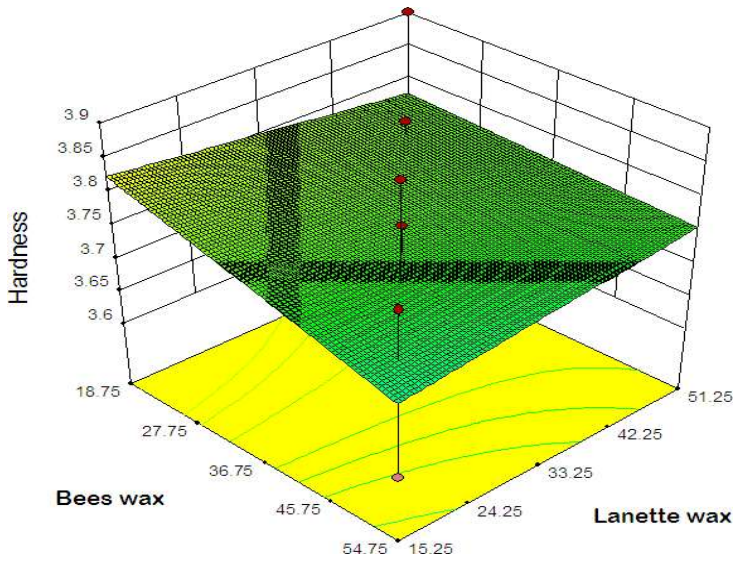

Figure 6: Response surface plot showing the influence on Hardness.

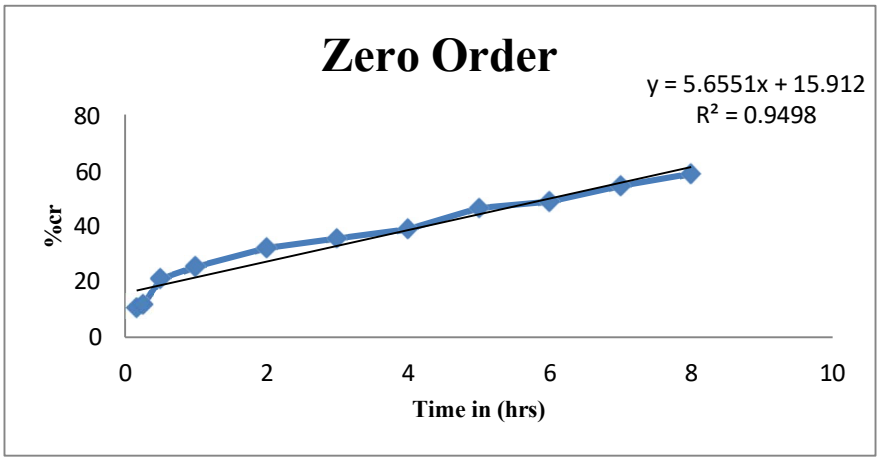

Figure 7: Zero order plot of F7 formulation

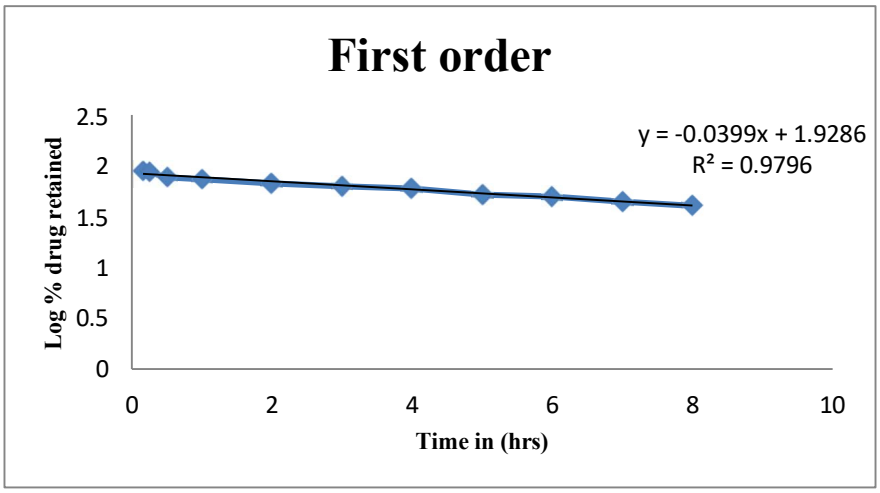

Figure 8: First order Plot of F7 formulation

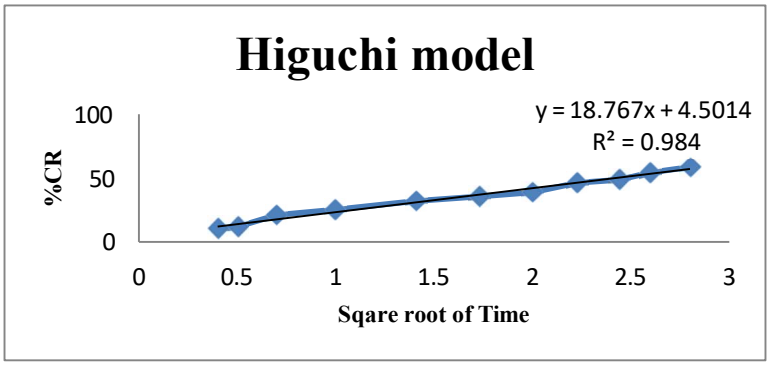

Figure 9: Higuchi's release kinetics of F7 Formulation

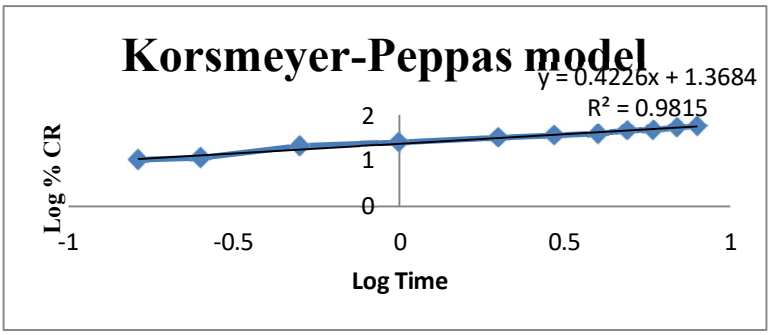

Figure 10: Korsmeyer-Peppas release kinetics of F7 formulation

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