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Novel Drug Delivery System To Enhance The Release Of Drug With Narrow Absorption Window

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ABSTRACT

The project aims towards development of a sustained release film to minimize the frequency of dosing and to enhance the efficacy of the drug with narrow absorption window. These drugs that are absorbed from a specific region (most notably first part) of the gastrointestinal tract. The drugs such as acyclovir gets absorbed in the upper tract of GI. The purpose of a sustained release dosage form is to keep therapeutic medication levels in the blood or tissues for a longer length of time. Attempting to acquire zero order release from the dose form is typically the way to go. Floating system is not feasible for those drugs that have solubility problems in gastric fluids. Drugs that are not stable at gastric pH are not suitable candidates to be formulated as NDDS. Drugs that irritate the mucosa. The drugs, which have multiple absorption sites in the gastrointestinal tract and are absorbed throughout gastrointestinal tract, which under significant first pass metabolism, are not desirable. Development of sustained release film possessing gastric retention capabilities. To achieve more predictable and increased bioavailability, Reduction in dosing frequency, reduced fluctuation in circulating drug levels, increased patient compliance, avoidance of night time dosing, more uniform effect and reduction in gastrointestinal (GI) irritation and other dose-related side effects. It can be concluded that the film enclosed in a capsule will swell and remain mucoadhesive in the GI and release APIs over a period of 12 hours there by increasing the bioavailability of Acyclovir and dexamethasone.

Keywords: NDDS, GI, DoE, GRDDS

INTRODUCTION

Oral sustained-controlled release formulations are an attempt to release the medicine slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for an extended period of time. Such a drug delivery would be held in the stomach and release the medication in a controlled way after oral administration, so that the drug may be delivered constantly to its absorption sites in the gastrointestinal system (GIT). After These drug delivery systems primarily suffer from two disadvantages: a short gastric retention time (GRT) and an unpredictable short gastric emptying time (GET), which can lead to incomplete drug release from the dosage form in the absorption zone (stomach or upper small intestine), resulting in decreased efficacy of the administered dose. In order to develop a site-specific, orally-administered, controlled-release dosage form, it is desirable to obtain a longer stomach residence time with the drug administration. Prolonged stomach retention enhances bioavailability, prolongs the time of drug release, decreases drug waste, and improves the solubility of

drugs that are less soluble in an environment with a high pH. Also, longer gastric retention time (GRT) in the stomach might be favourable for local action in the upper portion of the small intestine, such as peptic ulcer therapy, etc. (1,2)

Targeting site-specific medication release in the upper gastrointestinal tract (GIT) for local or systemic effects is the objective of gastroretentive drug delivery. The gastric retention time (GRT) of pharmaceuticals is greatly increased when gastroretentive dosage forms remain in the stomach for extended durations. Several gastroretentive drug delivery approaches have been designed and developed over the past few decades, including: high density (sinking) systems that are retained in the bottom of the stomach, low density (floating) systems that cause buoyancy in gastric fluid, mucoadhesive systems that cause bioadhesion to stomach mucosa, and unfoldable, extendable, or swellable systems that limit emptying of the dosage forms. (3, 4)

Factors controlling Gastric Retention of Dosage forms.

The anatomy and physiology of the stomach contain aspects that must be addressed during the creation of gastroretentive dosage forms. For particles to pass past the pyloric valve into the small intestine, their size must be between 1 and 2 millimetres. Gastric retention time (GRT) of oral dosage forms is controlled by density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity, and individual illness conditions (e.g. chronic disease, diabetes etc.) Anticholinergic medications (e.g., atropine, propantheline), opiates (e.g., codeine), and prokinetic agents (e.g. metoclopramide, cisapride.)Important characteristics include the drug's molecular weight and lipophilicity in relation to its ionization state. (5,6)

Approaches to Achieve Gastric Retention

- High density (sinking) method or non- floating drug delivery system
- Floating medication delivery systems
- Microballoons / Microspheres with a Hole
- Bioadhesive or mucoadhesive methods for medication delivery
- Super porous hydrogel systems
- Magnetic Methods
- Floating Drug Delivery System (FDDS)

Film Dosage forms

In general, a thin film is a layer of polymer that is thin and flexible, with or without a plasticizer [. Since they are naturally thin and flexible, the patient may regard them as less intrusive and more acceptable. The thin film is comprised of polymeric matrices that satisfy several criteria for usage as an effective drug release platform. Thin films are fundamentally ideal options for targeting sensitive sites, which may not be viable with tablets or liquid formulations. Thin films have demonstrated the capacity to accelerate the start of therapeutic action, decrease dosage frequency, and boost medication effectiveness. Similarly, thin films may be effective for minimising pharmacological adverse effects and proteolytic enzyme-induced extensive metabolism. Ideal thin films must possess desired characteristics such as adequate drug loading capacity, a rapid dissolving rate or a prolonged residence period at the site of administration, and adequate formulation stability. In addition, they must be non-toxic, biocompatible, and degradable.

It is superior to existing conventional dosage forms in terms of increased bioavailability, patient compliance, and patent extension of active pharmaceutical ingredients (API). In addition, thin film formulations provide various benefits, including (a) easy administration via non-invasive methods, (b) simplicity of fabrication and transportation, and (c) cost-effectiveness in formulation development. The availability of a vast variety of appropriate polymers and a paradigm change in manufacturing techniques have enabled the development of a vast array of thin films. As a new

drug delivery dosage form, a thin film is gaining favour and acceptability in the pharmaceutical industry. (7, 8, 9, 10, 11)

Polymeric film containing drug later encapsulated in capsule could be a potential work for anti-vial drug in combination with a corticosteroid fot its anti-inflammatory properties. Literature review shows some data as follows. Bashant Kumar Sah et. al. developed a gastro retentive sustained release film enclosed in a capsule using design for Losartan Potassium. The film was prepared by solvent cast method The film thickness ranged 0.20mm to 0.30 mm with Folding endurance above 150%, elongation minimum was 4.750% to 6.667%. The % Drug contest was observed via UV absorbance and found to be at 98% and surface pH at 7.0. The release rate of eight different prototypes were ranged from 90.2% to 101.24 % at 24 hours dissolution study. Coating with ethyl cellulose acted as a barrier to penetrate the aqueous medium to the formulation and increased the dissolution time. Sustained release films showed no change in appearance, drug content and dissolution profiles. (12)

P. Shailaja and G. Loknadh developed a gastro retentive mucoadhesive film of Ritonavir was developed. The % drug content in films was 87% to 93% with folding endurance 179 to 190 times. Swelling index from 83.16% to 111.57%. The sustained release film had a release of 99.08% at 12 hours showing in-vitro unfolding behaviour was found to be within 14-18 seconds. It was observed that as the HPMC K15M concentration is increased with an increase in the prolonged activity, as PVA concentration increased, there is no effect on the drug release.(13)

The current research aimed to develop a gastro retentive formulation for Acyclovir and Dexamethasone in order to increase the optimal bioavailability. Gastric emptying time in humans, which is normally 2-3 hours through the main absorption area (stomach or upper part of intestine), can result in incomplete drug release leading to diminished efficacy of administered dose. A formulation was made in film form which was encapsulated in a capsule to be administered orally. The capsule will dissolve within 15 to 30 min after oral administration, the film swells and opens and adheres to the mucoadhesive lining of the stomach. If not, the film will retain in gastic area for longer time for sustained release of drugs in stomach over a period of 8 to 12 hours. As Acyclovir has a half-life of only 3 hours and only 20% of the drug is absorbed and the rest is excreted unused.

MATERIAL AND METHOD

Film Formulation Development

For Prototype development, different Polymers like Agar-Agar, Guar Gum, Xanthan Gum, Carrageenan gum and Sodium alginate; Hydroxy Propyl Methyl Cellulose, Glycerin and Methyl Cellulose were used as Plasticizers; Stevia, Sucrose and Honey were used as Sweeteners; Water was used as Solvent. As the project is aimed towards sustained release of Acyclovir and dexamethasone, the technique used was to make a sustained release film which will be overlayed by an immediate release film. This will help the patient in two ways, one that patient can have immediate effect of anti-viral and anti-inflammatory properties from both APIs from the immediate release film causing patient compliance and second by sustained release film, as the API is release in prolonged manner, both bioavailability and effectiveness is increased causing long lasting effect and low dosing of formulation. Films were prepared by solvent/vehicle evaporation techniques.

Preparation of Film

Sustained Release Film (SRF)

Required quantity of vehicle was measure and transferred to a beaker and kept on mixing using an overhead mixer at 150 RPM per minute. The beaker was covered with aluminum foil to protect from environmental contamination. Required quantity of Acyclovir was weighed accurately and slowly added to the beaker main phase. It was made sure that acyclovir was completely dissolved. A side phase was prepared with ethanol in a beaker. Dexamethasone was added to this side phase and mixed thoroughly and dissolved. To the main phase was added other inactive excipients and mixed to form a homogenous mixture. With continuous mixing in main phase, side phase was added slowly and mixed. The mixed phase was made uniform. Mixing was stopped and this formulation was kept at Room temperature. Pour the formulation on a flat non-stick surface and keep in over at 75°C for drying. Allow to dry and remove the film from the glass surface.

Immediate release Film (IRF)

Required quantity of vehicle was measure and transferred to a beaker and kept on mixing using an overhead mixer at 150 RPM per minute. The beaker was covered with aluminum foil to protect from environmental contamination. Required quantity of Acyclovir was weighed accurately and slowly added to the beaker main phase. It was made sure that acyclovir was completely dissolved. A side phase was prepared with ethanol in a beaker. Dexamethasone was added to this side phase and mixed thoroughly and dissolved. To the main phase was added other inactive excipients and mixed to form a homogenous mixture. With continuous mixing in main phase, side phase was added slowly and mixed. The mixed phase was made uniform. Mixing was stopped and this formulation was kept at Room temperature. Add this mixture on the Sustained release film and allow to dry at 75°C in oven. Make sure the film is dry before removing it. Remove the film from the glass surface and check for their physiochemical properties of the two films joined together.

Physiochemical properties:

Thickness:

The thickness of the different films was measured using a calibrated dial gauge. Thickness was measured by placing each film between the anvil and the presser foot of the dial gauge in 5 different locations and the average thickness was calculated.

Uniformity of Weight:

Each film was individually weighed on analytical balance (Aczet CY 224C) and average weight of 3 films was found. A large difference in weight denotes the non-uniform distribution of drug in the film.

Percent Elongation:

When the sample films are subjected to tensile stress, deformation of the films occurs resulting in stretching or elongation of sample. It is performed to predict the ductility of polymer. It was calculated by formula:

$$\%\ Elongation = \frac{Increased\ length\ \times 100}{Original\ length}$$

Folding Endurance:

To determine folding endurance, a portion of film was cut and repeatedly folded at the same point till it breaks. The number of times the film could be folded at the same point without breaking indicates the folding endurance value.

Swelling Index:

Simulated saliva solution was used to check the swelling studies of films. Initial weight of film was determined and was placed in pre weighed stainless steel wire mesh. This mesh containing film was then dipped into simulated saliva solution. Increase in the weight of film was noted at constant pre-determined time intervals until no more increase in weight. Degree of swelling was determined by these parameters:

Degree of swelling = final weight (wt) – Initial weight (w0)/ Initial weight (w0)

Where,

Wt = weight of film at time interval t,

w0 =weight of film at time 0.

Surface pH:

Either highly acidic or highly basic pH of film would cause discomfort on administration. To know the surface pH of the film, the film was placed in a Petri dish and was moistened with 0.5 mL of distilled water and kept for 30 sec. The surface pH was measured by touching pH meter electrode on the surface of the swollen films.

Disintegration Time:

In vitro dispersion time was measured by Petri dish method. A film was dropped in culture dish of 10 cm in diameter, containing 10 mL of simulated salivary fluid. The Dispersion time was measured in seconds.

Drug Content:

Drug Content was determined by using HPLC. Prepared film were analysed as per HPLC method stated above. The prepared solution was measured for absorbance by using Absolute ethanol as blank. % Assay was calculated by using following formula;

$$\%\ Assay = \frac{Sample\ Absorbance}{Standard\ Absorbance} \times 100$$

In-Vitro Drug Release:

The In-Vitro Drug Release study was performed by using Dissolution apparatus. USP Type I Apparatus i.e. Basket type was used for Dissolution studies. The Prepared film was kept in a capsule and this capsule was kept in a basket and the shaft the dipped in 900 ml of 0.1 N HCL solution. 5 ml of aliquots at different time intervals was removed at 0, 10, 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours and to maintain the sink conditions 5 ml of fresh dissolution media was replaced. The aliquots were measured for Acyclovir and Dexamethasone content using HPLC technique. The method for HPLC analysis for simultaneous analysis of Acyclovir and Dexamethasone were developed prior to start of formulation development. The method was validated as per ICH guidelines.

RESULTS AND DISCUSSION

As the research aims at developing a film formulation kept in a capsule and to be taken orally, the initial development aims at making a film that can keep both the APIs and to be smooth and has good swelling index. Prototype development was done to make 8 different film formulation as below:

Table 1. Prototype development.

Films		**% w/w**							
Category	**Ingredients**	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
Active Constituent	Acyclovir	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Active Constituent	Dexamethasone	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Polymer	Carbomer 974	1	-	-	-	1	-	-	-
Polymer	Carbomer 940	-	1	-	-	-	1	-	-
Polymer	CMC	-	-	1	-	-	-	1	-
Polymer	HPMC K4M	-	-	-	1	-	-	-	1
Lubricity	PEG 300	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Plasticiser	Transcutol HP	50	50	50	50	-	-	-	-
Plasticiser	Propylene Glycol	-	-	-	-	50	50	50	50
Solvent	Water (qs to 100)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

The prepared films were dried as per predetermined method and oven dried for 24 hours.

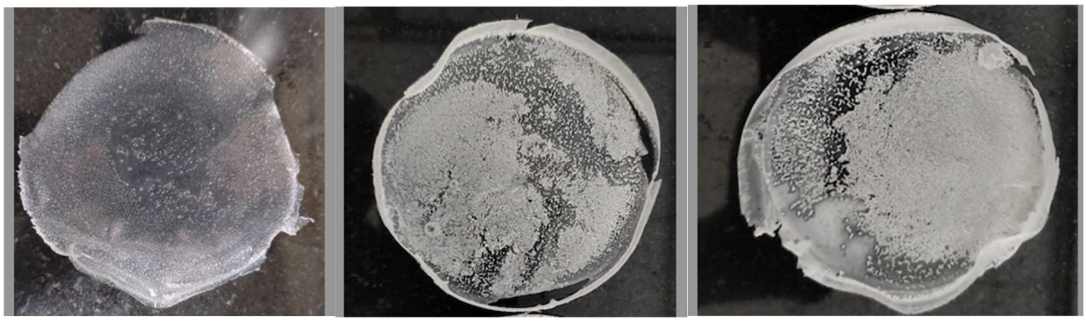

Figure No. 1: Represents a) F4, b) F5, c) F6 prototype formulaitons.

In all the prototypes, there was some greasy layer on the top of film. The possible cause was PEG 300. To confirm this, a film was prepared without the PEG 300 and the film was found to be smooth. It was concluded that PEG 300 was not required in this formulation. Also, it was observed that Propylene glycol formulation i.e. F5-F8 had longer drying time causing to leave PG stains on the film. PG also made the formulation gel like consistency causing low flowability properties. It was not an ideal choice to make the film with. It was analyzed that HPMC K4M and Carbomer 974 were the best fit among all the 8 formulations and transcutol HP was the choice of plasticizer for further analysis. The formulation development was to be done based on Quality by Design technique, Design Expert software was used to initiate the polymer choice and concentrations for film making. As the concentration of polymer had a direct impact on the drug release.

Organoleptic properties were studied. Out of the eight films prepared prototype F4, F5 and F6 were smooth and were able to peal of, rest of the prototype did not produce a film smooth enough to be considered. It was understood that Transcutol P produced a film with HPMC K4M that had some higher elasticity and choose for further prototype development. A design expert software version 13.0.5.0 was used to determine run order for further prototype evaluations. Using the design expert software, variables and critical evaluation parameters were uploaded and a technical analysis was plotted using Response Surface Central Composite model. with design designation as L8 (3^4), two different categories and three different levels, central composite model gave a eight-run prototype development formulation. The two categories selected were Carbomer 974P and HPMC K4M lower and higher concentration from 1% to 5% and 4% to 7% respectively and response was drug release profile. Below is the table obtained from central composite run order:

Table No. 02

Films		**% w/w**							
Category	Ingredients	RO1	RO2	RO3	RO4	RO5	RO6	RO7	RO8
Active Constituent	Acyclovir	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Active Constituent	Dexamethasone	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Polymer	Carbomer 974	1.7	1.5	1	0.3	0.5	0.5	1	1.5
Polymer	HPMC K4M	1	0.5	1.7	1	1.5	0.5	0.3	1.5
Plasticizer	Transcutol HP	50	50	50	50	50	50	50	50
Solvent	Water (qs to 100)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Films were prepared and subjected to analysis for its Physiochemical properties.

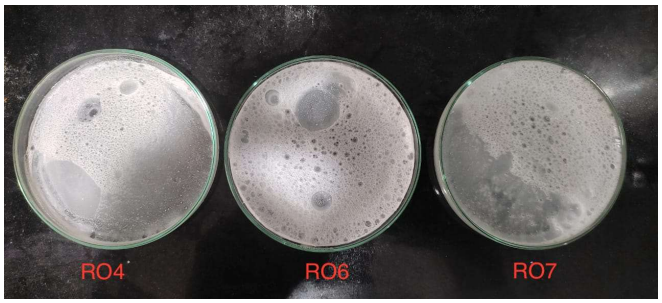

Fig 2: Films were prepared and characterized.

All the 8 films were characterized for Weight, thickness, % elongation, Folding endurance, Surface pH, Disintegration time, Degree of swelling.

The data is given as below:

Table No. 03

Batches	Weight (gm) (4 x 2 cm)	Thickness (um)	% Elongation	Folding Endurance	Surface pH
RO1	0.71	102.2	102.75	153	7.02
RO2	0.695	101.3	103.29	154	7.23
RO3	0.703	101.4	101.43	145	7.12
RO4	0.652	96.4	112.03	149	7.22
RO5	0.743	107.3	112.5	124	7.13
RO6	0.721	104.8	104.21	194	7.21
RO7	0.689	98.3	106.39	135	7.10
RO8	0.733	105.5	107.33	103	7.01

More or less, all the film possessed similar characteristics with respect to weight, thickness and % elongation. Highest folding endurance was seen in RO6 with 194 value. Surface pH was ranged between 7.01 to 7.23. Highest % elongation was seen in RO5 which contains 1.5% of HPLC K4M polymer giving it the ability to stretch

Table No. 04 Degree of Swelling

Batches	Initial Weight (mg)	Final Weight (mg)	Degree of Swelling
RO1	0.71	0.734	0.03
RO2	0.695	0.723	0.04
RO3	0.703	0.7423	0.06
RO4	0.652	0.693	0.06
RO5	0.743	0.779	0.05
RO6	0.721	0.742	0.03

RO7	0.689	0.71	0.03
RO8	0.733	0.758	0.03

All the prototypes more or less had the same degree of swelling based on it concentration HPMC conc. To know the amount of drug in a 4 x 2 cm cut film, HPLC study was done and it was found that the range of drug for Acyclovir and Dexamethasone were 47 mg to 53 mg and 3 mg to 7 mg respectively. Dissolution studies were performed as per method mentioned in Material and method using size '00' capsule. The film was folded in a Zig Zag manner so that upon capsule dissolving, the film could open up and the APIs are dispersed in controlled manner.

Table No. 05 % Drug Release – Acyclovir

% Drug Release – Acyclovir								
Time (hrs)	**RO1**	**RO2**	**RO3**	**RO4**	**RO5**	**RO6**	**RO7**	**RO8**
0	0	0	0	0	0	0	0	0
0.5	3.54	5.43	6.44	6.34	5.65	6.12	6.95	3.43
1	16.93	17.98	15.22	17.55	16.32	13.67	16.43	10.21
3	22.45	26.43	33.54	43.56	23.55	25.22	25.22	18.90
6	42.64	45.65	46.21	64.33	46.76	44.76	45.35	35.64
8	53.23	57.33	51.55	75.87	59.21	62.57	54.32	45.94
12	61.66	66.12	73.58	95.36	81.24	85.23	75.45	64.21

Table No. 06 % Drug Release – Dexamethasone

% Drug Release – Dexamethasone								
Time (hrs)	**RO1**	**RO2**	**RO3**	**RO4**	**RO5**	**RO6**	**RO7**	**RO8**
0	0	0	0	0	0	0	0	0
0.5	2.43	3.36	5.44	9.34	6.56	7.69	6.44	5.20
1	8.54	10.45	14.23	22.34	18.32	18.98	12.34	10.55
3	15.65	16.09	19.88	39.20	32.40	35.49	16.45	16.45
6	32.12	34.23	39.40	60.54	55.43	57.21	34.65	25.43
8	44.65	48.93	58.43	78.54	62.95	65.94	53.65	50.32
12	64.62	68.55	77.97	92.58	82.64	87.21	71.52	69.36

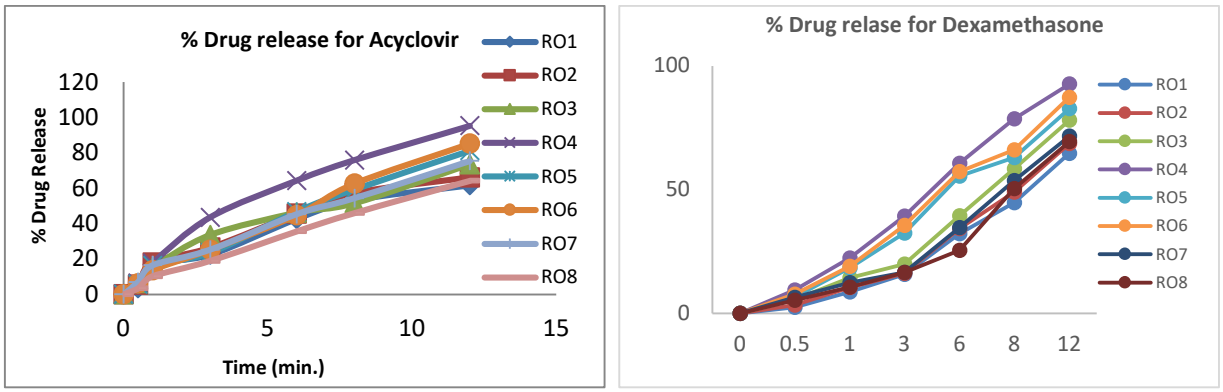

Figure No. 03 The Drug Release

The release range for Acyclovir is 61.66% to 95.36% the release range fir Dexamethasone is 64.62% to 92.58% Run order 4 had the highest release with a release of 95.36 and 92.58% for acyclovir and dexamethasone. The problem with RO4 was that the film size decrease significantly and therefore the due to no mucoadhesiveness property thereafter, the film will tend to pass the GI quickly and the actual adsorption will be very low.

Data revealed from Design expert studies were compared for actual data and predicted data from software as below:

Table No. 07 Acyclovir - Actual and Predicted values for drug release study

Run Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance	Influence on Fitted Value DFFITS	Standard Order
1	**61.66**	**60.63**	1.03	0.372	0.426	0.388	0.036	0.299	6
2	**66.12**	**65.91**	0.2084	0.378	0.086	0.077	0.002	0.06	2
3	**73.58**	**73.85**	-0.2705	0.372	-0.112	-0.1	0.002	-0.077	8
4	**95.36**	**90.08**	5.28	0.372	2.176	8.418(1)	0.936(2)	6.485(2)	5
5	**81.24**	**84.8**	-3.56	0.378	-1.474	-1.754	0.439	-1.366	3
6	**85.23**	**86.95**	-1.72	0.378	-0.713	-0.673	0.103	-0.524	1
7	**75.45**	**76.86**	-1.41	0.372	-0.582	-0.539	0.067	-0.416	7
8	**64.21**	**63.76**	0.4495	0.378	0.186	0.167	0.007	0.13	4

The results were very much comparable for actual and predicted values from the software for drug release of formulation RO6 –Acyclovir.

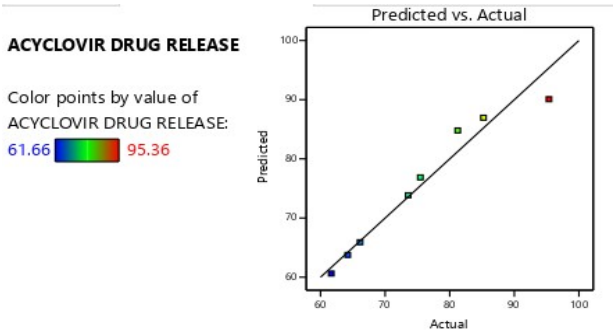

Figure No 04. Actual vs Predicted dissolution drug release study for acyclovir

Table No. 08 Dexamethasone - Actual and Predicted values for drug release study.

Run Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance	Influence on Fitted Value DFFITS	Standard Order
1	**64.62**	**64.24**	0.3791	0.372	0.15	0.134	0.004	0.103	6
2	**68.55**	**67.17**	1.38	0.378	0.549	0.507	0.061	0.395	2
3	**77.97**	**77.74**	0.2322	0.372	0.092	0.082	0.002	0.063	8
4	**92.58**	**89.37**	3.21	0.372	1.268	1.377	0.318	1.061	5
5	**82.64**	**86.45**	-3.81	0.378	-1.511	-1.833	0.462	-1.428	3
6	**87.21**	**85.12**	2.09	0.378	0.831	0.801	0.14	0.624	1
7	**71.52**	**75.87**	-4.35	0.372	-1.721	-2.412	0.586	-1.858(1)	7
8	**69.36**	**68.5**	0.8636	0.378	0.343	0.31	0.024	0.242	4

The results were very much comparable for actual and predicted values from the software for drug release of formulation RO6 – Dexamethsone.

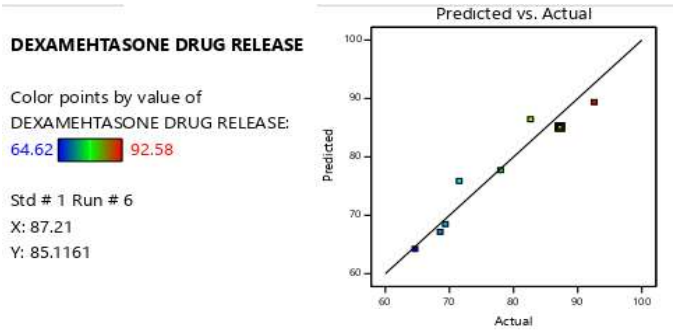

Figure No.05 Actual vs Predicted dissolution drug release study for Dexamethasone

It has been previously reported that the median bioavailability of oral Acyclovir (400mg) was 21.5% (95% CI, 17.9 to 33.2%). As the bioavailability is low for oral tablet of Acyclovir. Oral acyclovir has an average plasma half-life of three hours and is eliminated primarily by renal mechanisms. Peak plasma concentrations occur 1.5 to 2.5 hours after administration and the oral bioavailability is 15 to 30 percent. As the half-life is low, the drug concentration is kept at 400 mg. Therefore, out of 400 mg only 21.5% is used, i.e. 86 mg is actually absorbed in the plasma. This loss of drug is the point where we decided to make a more efficient technique where the drug is absorbed slowly in stomach over a period of at least 8-12 hours. It has been previously reported that a drug enclosed in a film like cross linked polymeric chain, release the drug over a period of hours. As demonstrated in dissolution studies, the drugs from the film is release over a period of 12 hours which inturn will have a higher half life as the drug will be continuously released from the film.

RO6 has a % drug release of 85.23% and 87.21% for Acyclovir and Dexamethasone respectively. The film swelling in the dissolution media was appropriate so that the film open up completely and keep steady in the stomach and does not pass the GI easily. Due to the mucoadhesive property of the polymers used, the film be release the drug continuously. HPMC tends to dissolve faster compared to carbomer 974, this is because HPMC is more hydrophilic comparately. This property benefits our research with intentionally medium release of both APIs in GI and later slow release from carbomer film. This slow and fast release combination will act as an Intermediate release and delayed or sustained release. Closing statement would be a method was developed to increase the bioavailability of Acyclovir in combination dexamethasone.

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