INNOVATIVE MICROSPHERE BASED DELIVERY OF DEFLAZACORT USING NATURAL AND SYNTHETIC POLYMERS -PREPARATION AND INVITRO PERFORMANCE

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ABSTRACT

Drug delivery strategies including microspheres have been utilized to improve effectiveness, reduce toxicity, and improve patient compliance. Additional benefits of employing microspheres to deliver medications include targeted drug delivery at the intended location, increased bioavailability, and controlled release. Microsphere formulations offer an advantage over traditional tablet or capsule formulations in that they improve medicine absorption and reduce drug dosage frequency by expanding the surface area exposed to the absorption site. The corticosteroid deflazacort is used to treat Duchenne muscular dystrophy. Deflazacort microspheres were generated using the ionotropic gelation approach with different deflazacort to sodium alginate ratios and polymers such as chitosan, xanthan gum, and Eudragit S100. The particle size and yield percentage of Deflazacort microspheres were investigated. Drug content, flow properties, surface morphology, and entrapment efficiency were all found to be within permissible parameters. When compared to the other formulations, in vitro dissolving trials of the microspheres revealed that formulation F12, which comprises Eudragit S100 as a polymer, has the maximum drug release after 12 hours. According to the enhanced formulation's drug release kinetics, formulation F12 employs a Super case II transport mechanism and zero order drug release.

Keyword: SEM, Eudragit S100, Deflazacort microspheres, and an ionotropic gelation method.

1.INTRODUCTION

Oral administration is the most widely accepted route for drug delivery due to its convenience, ease of use, and improved patient compliance. However, conventional oral dosage forms are often associated with drawbacks such as short biological half-life, frequent dosing requirements, and fluctuations in plasma drug concentrations, which may compromise therapeutic efficacy and increase the risk of adverse effects. Controlled release drug delivery systems (CRDDS) have been developed to overcome these limitations by releasing the drug at a predetermined rate, thereby maintaining steady plasma concentrations, reducing dosing frequency, and improving patient adherence[1,2]. Deflazacort, an oxazoline derivative of

prednisolone, is a glucocorticoid widely used for the treatment of inflammatory and autoimmune disorders such as Duchenne muscular dystrophy, rheumatoid arthritis, asthma, and nephrotic syndrome[3]. Despite its therapeutic potential, Deflazacort exhibits limitations including a relatively short half-life and the need for frequent administration, which may reduce patient compliance and increase the likelihood of dose-related side effects. Developing a controlled release formulation of Deflazacort, particularly in the form of microspheres, offers a promising strategy to prolong its therapeutic action, reduce dosing frequency, and achieve better disease management[4,5]. Biodegradable natural polymers such as chitosan, gelatine, and sodium carboxymethyl cellulose (NaCMC) have been extensively studied for microsphere preparation due to their biocompatibility, safety, and ability to control drug release. Incorporation of Deflazacort into such polymeric microspheres can protect the drug from degradation, provide sustained release, and minimize inter-individual variability in drug absorption[5,6]. Therefore, the present work focuses on the formulation and evaluation of Deflazacort-loaded microspheres using natural polymers. The study aims to optimize the formulation parameters, characterize the microspheres in terms of size, morphology, drug entrapment, and release kinetics, and evaluate their potential to provide an effective oral controlled release delivery system for Deflazacort.

2.EXPERIMENTAL

Deflazacort is a synthetic glucocorticoid prodrug indicated for Duchenne muscular dystrophy in patients ≥2 years. It is a white crystalline compound that is rapidly absorbed after oral dosing. After oral administration deflazacort is de-acetylated by plasma esterases to the active 21-deflazacort which is further metabolized to inactive metabolites; elimination is mainly renal (~70%) with the remainder in feces, and most drug is cleared within 24 h. Pharmacodynamically it acts via glucocorticoid receptor–mediated anti-inflammatory and immunosuppressive effects and clinically has been shown (typical dosing ~0.9 $mg \cdot kg^{-1} \cdot day^{-1}$) to preserve muscle mass and delay progression of DMD symptoms. The chosen excipients support ionotropic-gelation microsphere formulation: chitosan ($(C_6H_{11}O_4N)_n$) is a biodegradable, cationic linear polyamine (pharmaceutical grade deacetylation ~90–95%) insoluble in water but soluble in dilute acids, bioadhesive and readily ionotropically cross-linkable with multivalent anions (e.g., TPP, alginate) and useful for sustained-release and mucoadhesive microspheres; sodium alginate ($(C_6H_7O_6Na)_n$) is a hygroscopic, water-soluble polysaccharide that forms calcium-crosslinked gels and provides matrix integrity and controlled release; calcium chloride ($CaCl_2$, MW 110.98 $g \cdot mol^{-1}$) is a highly water-soluble, deliquescent salt used as the calcium source to induce alginate gelation; xanthan gum is a water-soluble viscosity-building stabilizer employed to modify viscosity, suspension stability and release; and Eudragit S100 is an anionic, enteric polymer that is insoluble in gastric pH but dissolves at intestinal pH (>7), used for pH-dependent protection or delayed/targeted release. Together these materials enable formation of stable, crosslinked alginate/chitosan/xanthan microspheres with tenable entrapment efficiency and pH-dependent release characteristics suitable for oral controlled delivery of deflazacort.

3.MATERIALS AND METHODS

3. Materials and Methods

3.1 Materials

Deflazacort (pharma grade) was obtained from Glenmark Pharmaceuticals Ltd. Sodium alginate, chitosan, xanthan gum, and calcium chloride (LR grade) were procured from S.D. Fine Chemical Ltd., Mumbai. Eudragit S100 (LR grade) was purchased from Shreeji Chemicals, Mumbai. All other reagents and solvents used were of analytical grade.

3.2 Buffer Preparation

3.2.1 Preparation of 0.2 M Potassium Dihydrogen Orthophosphate Solution

A total of 27.218 g of monobasic potassium dihydrogen orthophosphate was accurately weighed and dissolved in distilled water, and the volume was adjusted to 100 mL.

3.2.2 Preparation of 0.2 M Sodium Hydroxide Solution

Eight grams of sodium hydroxide pellets were dissolved in distilled water and the final volume was made up to 1000 mL.

3.2.3 Preparation of pH 6.8 Phosphate Buffer

A measured volume of 250 mL of the 0.2 M potassium dihydrogen orthophosphate solution was mixed with 112.5 mL of the 0.2 M sodium hydroxide solution in a 1000 mL volumetric flask. The final volume was adjusted to 1000 mL using distilled water.

3.3 Pre-Formulation Studies

Pre-formulation studies were conducted to evaluate the physicochemical characteristics of Deflazacort and assess its suitability for microsphere formulation.

3.3.1 Melting Point Determination

The melting point of Deflazacort was determined to assess its purity and thermal stability. The temperature at which the drug exhibited a solid-to-liquid phase transition was recorded.

3.3.2 Solubility Studies

Excess drug was added to 10 mL of different buffer systems and stirred at 150 rpm for 24 h at 25 °C to reach equilibrium. The suspensions were filtered through a 0.45 µm PVDF membrane. The filtrates were appropriately diluted and analyzed by UV-Visible spectrophotometry to determine saturation solubility in each medium.

3.3.3 Determination of Absorption Maximum (λmax)

A primary stock solution of 1000 µg/mL was prepared by dissolving 10 mg of Deflazacort in pH 6.8 phosphate buffer. Serial dilutions were prepared to obtain a 10 µg/mL working solution.

This solution was scanned between 200–400 nm using a UV-Visible double-beam spectrophotometer. The λmax of Deflazacort was found to be 247 nm.

3.3.4 Evaluation of Flow Properties

Flow properties of the drug powder were assessed to ensure suitability for solid dosage form processing. Parameters related to powder flowability were measured to predict uniformity in mixing and filling operations.

3.3.5 FTIR Spectroscopic Analysis

Drug–polymer compatibility was evaluated using FTIR spectroscopy (Shimadzu 8400S). A 2% w/w sample with potassium bromide (KBr) was compressed into a transparent disc at 10,000 PSI. The disc was scanned ten times at a resolution of 2 cm^{-1} using Happ–Genzel apodization. Characteristic peaks were examined to identify possible interactions between Deflazacort and the polymers.

3.4 Preparation of Calibration Curve

A 1000 µg/mL stock solution was prepared by dissolving 10 mg of Deflazacort in 10 mL of pH 6.8 phosphate buffer. This was further diluted to obtain a 100 µg/mL secondary stock solution. Aliquots of 0.5–3 mL were transferred to 10 mL volumetric flasks and diluted to produce concentrations ranging from 5 to 30 µg/mL. Absorbance values were measured at the λmax, and a calibration curve was constructed. Linearity was confirmed by calculating the correlation coefficient (R^2).

3.5 Preparation of Deflazacort Microspheres

Deflazacort microspheres were formulated using the ionotropic gelation technique. Sodium alginate served as the primary polymer, while chitosan, xanthan gum, and Eudragit S100 were used as co-polymers. Calcium chloride acted as the cross-linking agent.

Initially, the required amount of sodium alginate was dissolved in 25 mL distilled water to obtain a uniform polymer solution. The weighed quantities of Deflazacort and selected co-polymers were added to the alginate solution and stirred at 800 rpm until completely dispersed. The mixture was extruded dropwise through a 22-gauge syringe needle into 100 mL of a 1% w/v calcium chloride solution under continuous stirring. Cross-linking was allowed to proceed for 60 minutes.

The formed microspheres were collected by filtration, washed with purified water, and dried at 40 °C for 12 hours. Formulations were optimized based on entrapment efficiency and in vitro drug release performance.

Table 1: Formulation design for Deflazacort microspheres using different ratios of drug and polymers

Formulation code / Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Deflazacort	30	30	30	30	30	30	30	30	30	30	30	30
Sodium alginate	100	100	100	100	100	100	100	100	100	100	100	100
Chitosan	15	30	45	60	--	--	--	--	--	--	--	--
Xanthan gum	--	--	--	--	15	30	45	60	--	--	--	--
Eudragit S100	--	--	--	--	--	--	--	--	15	30	45	60
Calcium chloride	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

4.RESULTS AND DISCUSSION

The solubility of the drug is more in 6.8 pH Buffer than the other buffers. The maximum absorbance of the Deflazacort was found to be at 247 nm. Hence the Wavelength of 247 nm was selected for analysis of drug in dissolution media.

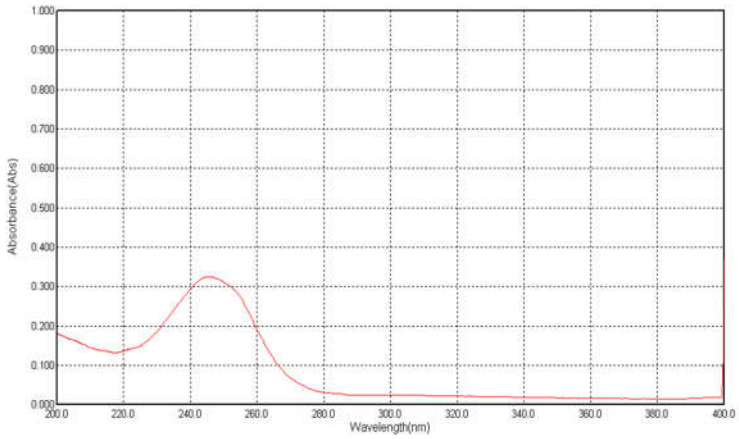

Figure 1: UV spectra of Deflazacort at 247 nm

From the drug excipient compatibility studies we observed that there are no interactions between the pure drug (Deflazacort) and optimized formulation (Deflazacort+ excipients) which indicates there are no physical changes.

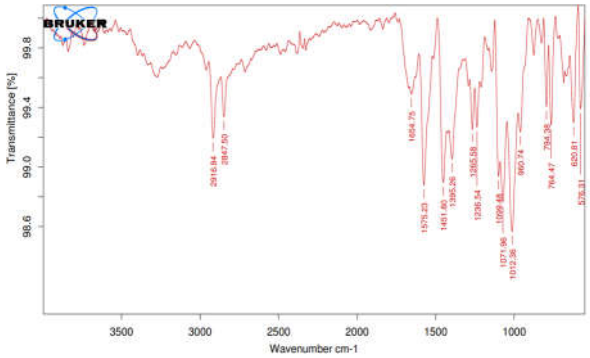

Figure 2: IR spectra of pure Deflazacort

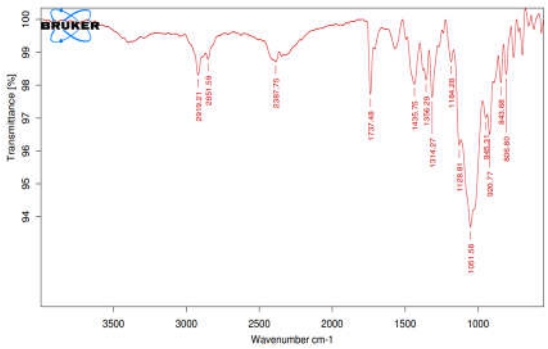

Figure 3: IR spectra of optimized formulation

The formulations F1 to F12 found to have varying bulk density, tapped density, compressibility index and Hausner's ratio which ranged from 0.305±0.02gm/cc to 0.341±0.01gm/cc, 0.418±0.02gm/cc to 0.457±0.01gm/cc, 12.12±1.18% to 20.27±1.12% and 1.12±0.01 to 1.19±0.02 respectively. The observed values were within I.P limits and also demonstrate good flow property for the developed formulation

Table-2: Characterization of Deflazacort microspheres

Parameter	Bulk density (gm/cc)	Tapped density (gm/cc)	Hausner's ratio	Compressibility index
F1	0.305±0.02	0.418±0.02	1.18±0.01	20.27±1.12
F2	0.312±0.01	0.425±0.01	1.19±0.02	18.55±1.09
F3	0.327±0.02	0.439±0.02	1.17±0.01	17.46±1.08
F4	0.329±0.01	0.445±0.01	1.16±0.02	15.34±1.14
F5	0.310±0.02	0.410±0.01	1.21±0.01	18.42±1.15
F6	0.319±0.01	0.429±0.02	1.19±0.01	19.21±1.19
F7	0.326±0.02	0.436±0.01	1.17±0.02	18.58±1.12
F8	0.334±0.01	0.448±0.01	1.15±0.01	16.47±1.18
F9	0.318±0.02	0.421±0.02	1.18±0.02	17.98±1.12
F10	0.327±0.01	0.436±0.01	1.16±0.01	15.52±1.16
F11	0.335±0.02	0.446±0.02	1.14±0.02	14.34±1.11
F12	0.341±0.01	0.457±0.01	1.12±0.01	12.12±1.18

The formulations F1 to F12 found to have varying particle size, percentage yield, entrapment efficiency and drug content which ranged from 200.01±1.54 µm to 230.62±1.67µm, 91.19±1.48% to 98.62±1.69%, 48.47±1.42% to 78.45±1.20% and 92.56±1.42% to 99.15±1.15% respectively.

Table -3: Particle size, Drug Entrapment Efficiency of Deflazacort microspheres

Formulation Code	Particle Size (µm)	% Yield	Entrapment Efficiency	Drug Content
F1	208.15±1.57	91.19±1.48	48.47±1.42	92.56±1.42
F2	210.74±1.25	93.43±1.57	54.48±1.36	94.48±1.54
F3	205.78±1.16	94.25±1.10	60.16±1.51	97.59±1.09
F4	220.15±1.67	95.18±1.06	66.24±1.48	97.78±1.10

F5	215.15±1.48	92.64±1.25	52.45±2.20	93.46±1.45
F6	210.18±1.57	94.75±1.18	58.16±2.14	95.78±1.20
F7	230.62±1.67	95.02±1.37	66.38±1.24	97.11±1.48
F8	205.78±1.56	96.36±1.45	71.54±1.36	98.96±1.05
F9	201.18±1.29	95.24±1.12	58.26±1.48	95.15±1.46
F10	205.62±1.48	97.48±1.05	69.18±1.12	97.36±1.24
F11	205.45±1.37	98.17±1.16	73.20±1.45	98.47±1.45
F12	200.01±1.54	98.62±1.69	78.45±1.20	99.15±1.15

The optimized formulation was evaluated for its surface morphology by using Scanning electron microscopy. The outer surface of the microspheres was found to be smooth. The surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. The particle size was found to be 200µm.

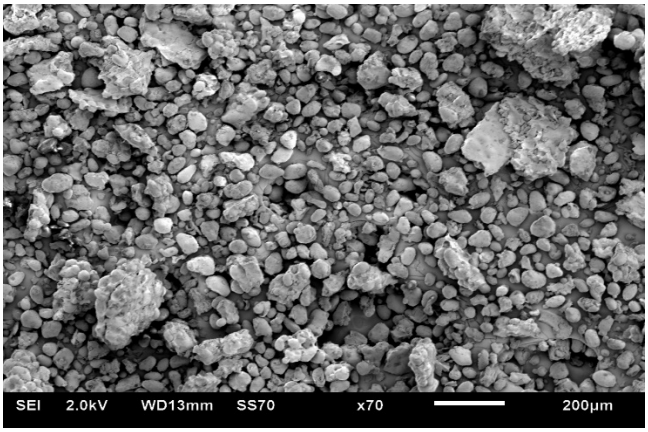

Figure 2 : Scanning Electron Microscopy analysis(SEM)

The formulations F1-F4 prepared with (ratios range 1:1, 1:2, 1:3 and 1:4) concentration of polymer like Pectin and drug release as shown in Table. As the polymer concentration was increases the time of drug release was increases. The formulations F4 showed burst effect and released 97.12±0.23% at the end of 12thhrs. The formulations F5-F8 prepared with (ratios range 1:1, 1:2, 1:3 and 1:4) concentration of polymer like HPMC K15M and drug release as shown in Table. The formulations F8, releases 98.41±1.07% at the end of 12th hr respectively.

The formulations (F9, F10, F11 and F12) were tried with Chitosan (ratios range 1:1, 1:2, 1:3 and 1:4) as retardant being insoluble in gastric pH. The formulations F12 was found to be 99.11±1.42% at the end of 12hrs The formulation F12 was made with the Chitosan in the drug polymer ratio of 1:4 and drug release was found to be 99.11±1.42% at the end of 12hrs with better drug release pattern, thus F12 was considered as optimized formulation.

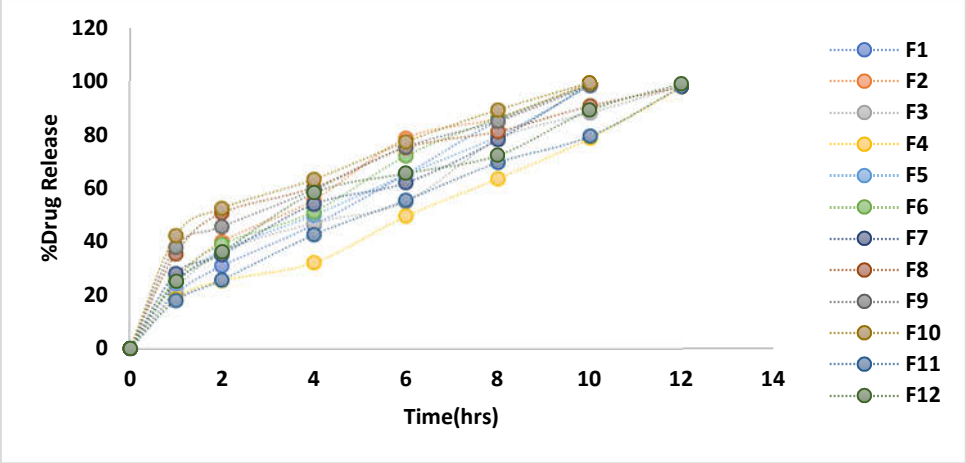

Figure-3 : *In vitro* dissolution profile of Deflazacort formulations F1-F12

The optimized formulation F12 has coefficient of determination (R^2) values of Zero order, First order, Higuchi and Korsmeyer Peppas of 0.933, 0.762, 0.990 and 0.616 respectively. A good linearity was observed with the zero order. The slope of the regression line from the Higuchi plot indicates the rate of drug release through mode of diffusion, and further confirms the diffusion mechanism. The data fitted into the Korsmeyer Peppas equation which showed linearity with slope n value of 1.160 for optimized formulation F12. This n value indicates the coupling of (swelling, polymer relaxation) diffusion and erosion mechanism. Thus, it indicates the drug release from the tablet follows Super case transport mechanism. The presence of swelling and cross linked polymers within the matrix structure might be responsible for the drug release controlled by more than one process. Thus, with regarded to release kinetics, the optimized batch F12 follows best fitted for zero order drug release with Super case II transport mechanism.

ZERO ORDER PLOT

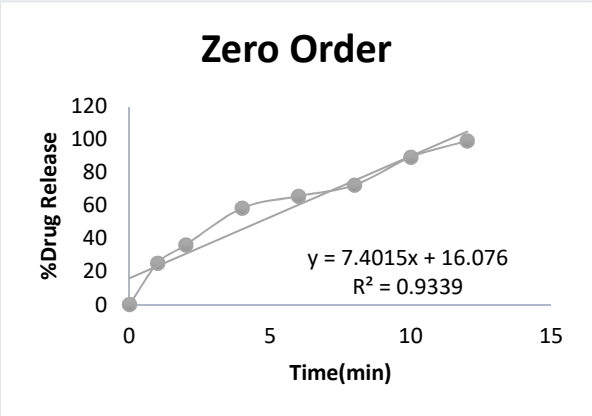

Figure 4: Optimized formulation zero order Plot of Deflazacort(F12)

FIRST ORDER PLOT

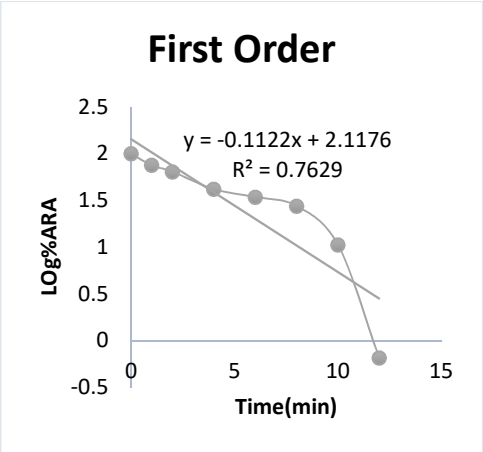

Figure 5 : Optimized formulation first order plot of Deflazacort (F12)

HIGUCHI PLOT

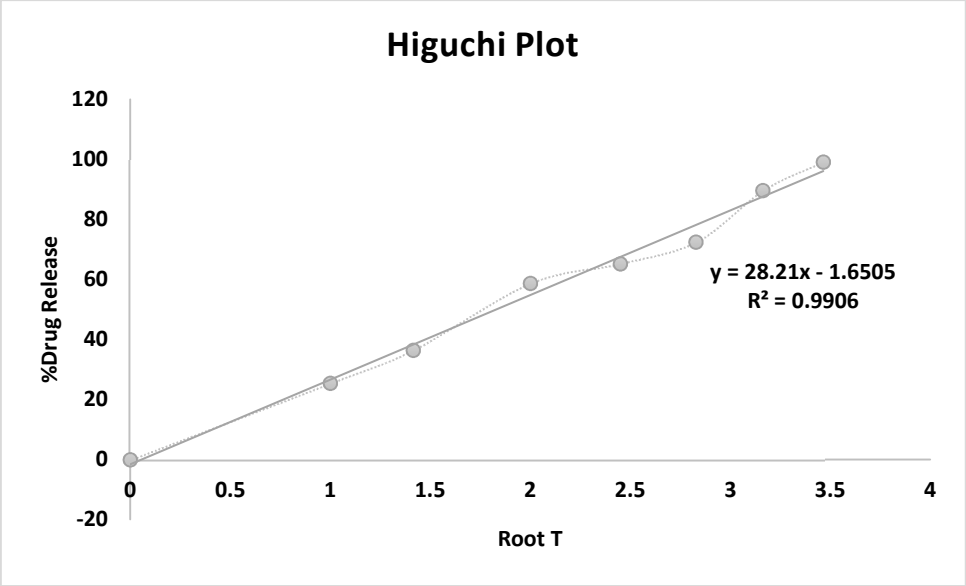

Figure 6 : Optimized formulation Higuchi plot of Deflazacort (F12)

PEPPAS PLOT

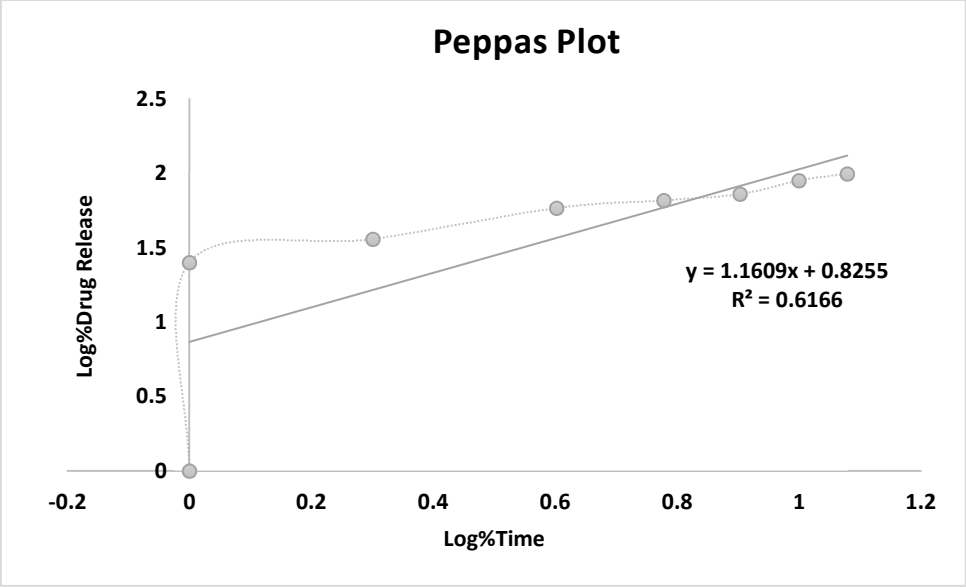

Figure 7: Optimized formulation Peppas plot of Deflazacort (F12)

Table 4: Co-efficient of determination and 'n' values of optimized formulation (F12)

	R^2 values				n values
Formulations	**Zero order**	**First order**	**Higuchi**	**Korsmeyer-peppas**	**Korsmeyer-peppas**
F12 Optimized	0.933	0.762	0.990	0.616	1.160

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