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DEVELOPMENT & EVALUATION OF PECTIN-BASED CONTROLLED POROSITY OSMOTIC PUMP FOR COLON-SPECIFIC DELIVERY SYSTEM

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ABSTRACT

A pectin based osmotic dosage form consisting of a enteric coated with a pH- dependent polymer is proposed for colonic specific delivery of drugs. Different approaches for colon-specific drug delivery have been studied over the last decade, including prodrugs, polymeric coating using pH-sensitive or bacterial degradable polymers and matrices. In this work, we present a new osmotic system to deliver active molecules to the colonic region, which combines pH-dependent and controlled drug release properties. The tablet core was constituted by drug (dexamethasone), pH modifier (citric acid) and pectin coated by an enteric polymer (Eudragit L 100-55). The pectin based colon-targeted osmotic pump was developed based on both the gellable property at acid conditions and colon-specific biodegradation of pectin. The SEM indicated that the pectin was accessible to enzymatic degradation which allowed the in situ formation of delivery pores for releasing drug under conditions that may be expected to pertain in the colon, the number of pore being dependent on the initial level of pore former in the membrane. Dexamethasone release from the developed formulation was inversely proportional to the osmotic pressure of the release medium. Thus the developed system was found to be a potential system for targeting and controlling the release of dexamethasone to the colon.

KEYWORDS: Pectin, dexamethasone, Eudragit L-100-55, osmotic tablet.

INTRODUCTION

Inflammatory bowel disease (IBD) is an ongoing or chronic health problem that causes inflammation and swelling in the digestive tract. The irritation causes bleeding sores called

ulcers to form along the digestive tract. This in turn can cause crampy, abdominal pain and severe bloody diarrhea.

There are two main types of inflammatory bowel disease: ulcerative colitis (UC) and Crohn's disease (CD). The diseases are very similar. In fact, doctors often have a hard time figuring out which type of IBD a person has. The main difference between UC and CD is the area of the digestive tract they affect. CD can occur along the entire digestive tract and spread deep into the bowel wall. In contrast, UC usually only affects the top layer of the large intestine (colon) and rectum. Medicine can control the symptoms of IBD in most women. But for people who have severe IBD, surgery is sometimes needed. Over the course of a person's life, the symptoms of IBD often come and go. With close monitoring and medicines, most people with IBD lead full and active lives.

A pectin based colon-targeted osmotic pump was developed based on both the gellable property at acid conditions and colon-specific biodegradation of pectin. The SEM indicated that the pectin was accessible to enzymatic degradation which allowed the in situ formation of delivery pores for releasing drug under conditions that may be expected to pertain in the colon, the number of pore being dependent on the initial level of pore former in the membrane. Dexamethasone release from the developed formulation was inversely proportional to the osmotic pressure of the release medium.

The parameter of membrane permeability complied well with literature data, confirming that osmotic pumping mechanism was the major principle of drug release. The effects of different formulation variables were studied to select the optimal formulation. Drug release was directly proportional to the initial level of pore former. Level of pH modifier (citric acid) affected the viscosity of pectin solution, resulting in the change of osmotic pressure in the core tablets.

The amount of pectin in core formulation had a profound effect on the amount of drug release. An optimal core formulation that benefited from suspending and osmotic effect of pectin has been developed. The enteric-coating membrane could prevent CA membrane containing pore former (pectin) from forming pore or rupture before SCF dissolution procedure, and no significant difference in release profiles could be found when the level of enteric-coating membrane differed. The osmotic tablets exhibited gastric and small intestine resistance but were susceptible to bacterial enzymatic attack, and the potential of pectin based

osmotic tablet as a carrier for drug delivery to the colon was confirmed in simulated physiological GIT conditions.

Thus the developed system was found to be a potential system for targeting and controlling the release of dexamethasone to the colon.

Experimental Materials and methods

Dexamethasone was obtained as a gift sample from R. P. Traders, Delhi. Pectin and triethyl citrate (TEC) were purchased from Sigma-Aldrich Co. Ltd. Citric acid and cellulose acetate (CA, 53.5–56 wt% acetyls content) was procured from Qualigens Fine chemicals (Mumbai). Pectin, talc and magnesium stearate were obtained from C.D.H. New Delhi. Eudragit® L100-55 was purchased from R¨ohm Pharm, Darmstadt, Germany. Silicified microcrystalline cellulose (SMCC, Pro-Solv® 90) was obtained as a gift sample from Forum Products Limited Noida. Acetone (AR Grade) was purchased from RFCL New Delhi. Solvents of reagent grade and double distilled deionised water were used in all experiments.

Preparation of core tablets

Dexamethasone was pre-mixed with a small amount of pectin by spatulation, followed by mixing manually for 10 min with the remaining pectin and other ingredients. The resultant powder mixture was sieved through 100 mesh screen and directly compressed into tablets using 8.0mm standard concave punches on a single punch tablet machine. The weight of each tablet was determined to be within the range of 120±5mg in order to maintain the relatively constant volume and surface area.

Microporous semipermeable membrane coating

Cellulose acetate in acetone containing different levels of pore forming agent (pectin) was used as coating formulation (Table 4.14). The weight gain was kept at12%. TEC (25% of total coating materials) acted as a hydrophilic plasticizer and was added to enhance the physical–mechanical property of cellulose acetate membrane.

The coating is carried out in pan coater provided hot air blower (Macro Scientific works, New Delhi, stainless steel pan, 50 cm diameter). The rotation rate of the pan was kept at 40 rpm. The coating was sprayed with the help of air less spray gun (Manik Radiators, Mumbai) at spray rate, 3 ml/min. The surface morphology of the coated tablets was a little bit rough even though the fine micronized pectin powder (400 meshes) was used. After coating, the

tablets were dried for 12 h at 50^0C to remove residual solvent.[7]

Enteric coating

Different concentrations of Eudragit® L100-55 were used to coat on the surface of microporous semipermeable membrane. The coating is carried out in pan coater provided hot air blower (Macro Scientific works, New Delhi, stainless steel pan, 50 cm diameter). The rotation rate of the pan was kept at 40 rpm. The coating was sprayed with the help of air less spray gun (Manik Radiators, Mumbai) at spray rate 3ml/min. The surface of osmotic tablet had a smooth and uniform appearance. Coated tablets were dried for 4 h at 40^0C.[7]

Evaluation

***In vitro* dissolution**

In vitro dissolution studies were carried out in USP XXV dissolution test apparatus (basket method) (Electolab TDL-08L). These studies carried out at 50 rpm and 37.5 ± 0.5^0. The tablets were tested for drug release for 2 hr in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with phosphate buffer pH 6.8(900 ml) and tested for drug release for 2 hr. Then the dissolution medium was further replaced with 100 ml phosphate buffer pH 7.4 with pectinase contained in 200-ml beaker, and immersed in water maintained in 900ml vessel, which in turn was in the water bath of the apparatus.[10]

5 ml samples were withdrawn at predetermined time intervals for period 18 hr and replaced with the equal volume of the same dissolution medium. The samples were filtered through Whatman paper filter and the concentration of the drug was obtained by measuring the absorbance at 242 nm using double beam UV-spectrophotometer (1700-E, Shimadzu). The content of drug was calculated using equation generated from calibration curve. The test was performed in triplicate. For study the effect of diluents, polymer, pore former and the ratio of pectin and citric acid the dissolution test was carried out in three phases.

Phase 1

To evaluate the effect of diluents, polymer and the ratio of pectin and citric acid formulation F1 to F5 were prepared (table 4.13). The prepared formulations were coated with microporous semipermeable membrane containing 25 % pectin as pore former. Dissolution carried out for formulations P1S2, P2S2, P3S2, P4S2 and P5S2 (table 4.19 & figure 4.12) in phosphate buffer 7.4 with pectinase to simulate the colonic environment.

Phase 2

To evaluate the effect of pore former formulation P4 was coated with various microporous semipermeable membrane formulas as S1, S2, S3 and S4 containing 15%, 20%, 25% and 30% of pore former pectin (table 4.20). Dissolution was carried out in phosphate buffer 7.4 with pectinase to simulate the colonic environment.

Phase 3

To evaluate enteric coating polymer, formulation P4S2 was coated with Eudragit® L100-55. Various concentration of Eudragit® L100-55 was used to coat on microporous semipermeable membrane as E1=8%, E2= 6% and E3=4% (table 4.21). Dissolution carried out in four steps, 2 hr in 0.1N HCl, 2 hr in buffer pH 5.0, 2 hr in buffer pH 6.8 and in last buffer 7.4 with pectinase to simulate the physiological condition in colonic environment.

RESULT AND DISSCUSSION

The most promising of the colonic drug delivery systems are those that depend on enzymatic action of colonic bacteria on polysaccharides. The polysaccharides that are under investigation as carriers for colon targeted drug delivery include pectin, amylase and pectin. Based on this information osmotic a tablet of dexamethasone was developed for effective and safe therapy for inflammatory bowel disease.

In- vitro release studies showed that pectin as a pore former in the semi permeable membrane of OSMOTIC TABLET is specifically degraded by micro flora of the colon and thereby results in an in situ formation of a delivery pores. The saturated solution of drug is delivered from these delivery pores at a relatively constant release rate for up to 18 hr in the colon. In present work, osmotic tablets containing dexamethasone were prepared to achieve the following goals:

- To prepare colon specific drug delivery with system with controlled release.
- To develop superior formulation with pronounced targeting potential to colon compared to conventional delivery system(s).

5.1. Pre formulation studies

5.1.1 Identification of drug

5.1.1.1 Melting Range

The melting range of drug was found to be within the range of 261^0C – 264^0C, which was in agreement with reported values indicating the purity of drug.

5.1.1.2 U.V. Spectroscopy

When solution of dexamethasone in methanol was scanned between 200 nm to 300 nm, the solution showed an absorption maximum at 239 nm. It was in agreement with the reported value i.e. 239 nm indicating the presence of dexamethasone.

5.1.1.3 F.T.I.R. Spectroscopy

The F.T.I.R. absorption spectrum of dexamethasone was recorded and found to be similar to the reference spectrum. The typical peaks of the spectrum were also interpreted. The results confirmed the test sample was dexamethasone.

5.1.1.4 Solubility studies

The drug was very practically insoluble in distilled water, sparingly soluble in acetone, methanol and in ethanol while slightly soluble in phosphate buffer pH 5.0, 6.8 and also in 0.1N hydrochloric acid. Low drug solubility in distilled water was probably due to its hydrophobic nature.

5.1.1.5 Partition coefficient

The partition coefficient of drug was 0.97 which indicated that drug is hydrophobic in nature.

5.1.1.6 Compatibility studies

There was no significant change in the peak behavior of functional group in pure drug and drug-polymer mixtures, when analyzed by the IR Spectroscopy, hence the drug and polymer combination was found compatible with each other.

5.2 Calibration curve of the drug

Calibration curve of dexamethasone in phosphate buffer pH 6.8 was found to follow Beer-Lambert law in range 1 to 20 µg/ml with R^2 value 0.9992. Calibration curve of dexamethasone in phosphate buffer pH 7.4 was found to follow Beer-Lambert law in range 1 to 20 µg/ml with R^2 value of 0.999.

5.3 Physicochemical parameters of formulations

All formulations were characterized for their physicochemical parameters like weight variation, hardness, thickness, Friability and drug content. Five formulations were prepared. The weight of the core tablet of the different formulation varied between mg 113.6 to 114.6 mg. The variation in the weight was within the range of ±5% complying with the

Pharmacopoeia's specifications. The hardness of core tablet varies with in the range of 10.3 to 8.02 kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all formulations, which is an indication of good mechanical strength. The drug contents varied between 98.05% - 99.02% in different formulations indicating content uniformity in the prepared tablet. All parameters were found within limits.

5.4 Formulation aspects

5.4.1 SEM of microporous semipermeable membrane

In order to study the changes in the membrane structure throughout the dissolution procedure and the mechanism of drug release from osmotic tablet, the membranes of coated tablets obtained after three step-dissolution studies, were investigated by SEM.

Before dissolution studies, no porous membrane structure was observed with the presence of different levels of pore former (pectin). The surfaces of coated tablets were yellowish and glossy and the membrane appeared to be integral and smooth with no visible imperfections. There was no evidence of formation of pores in the membrane in dissolution in 0.1N HCl, in buffer pH 5.0, in buffer pH 6.8. The results demonstrated that the enteric- coating membrane could prevent pectin incorporated in the CA film from dissolving in the 0.1NHCL and in buffer pH 5.0.

After phosphate buffer pH 6.8 dissolution studies, the enteric membrane dissolved, but pore was still not developed in the semipermeable membrane because of absence of bacterial enzymes which might degrade the pectin. Throughout the phosphate buffer pH 6.8 dissolution studies, no in situ formation of pores in the semipermeable CA membranes containing pectin took place.

After exposure to SCF release medium, formation of in situ pores in the membranes was observed, which possibly acted as an exit for the drug release.

The SEM study indicated that in situ formation of pores was possible in the thin structure of the semipermeable CA membrane containing pectin because of its biodegradability when meeting colonic bacteria. Moreover, it can be concluded that biodegradation of pore former (pectin) from the membrane (after coming into contact with the SCF environment) left behind the porous membrane for drug release. The numbers of pores were directly proportional to the initial level of pore former in the membrane.

5.4.2. Formulation aspects of core tablets

5.4.2.1. Effect of pectin: citric acid ratio on drug release

It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmotic agents for the release of water-insoluble drug.[1] Due to its high molecular weight and a linear unbranched structure, pectin is completely biodegradable, toxicologically harmless and low cost and exhibits an excellent gelation characteristic.[2] Hence the potential for pectin to be used as a polymeric osmotic agent in osmotic pump is obvious. The hydration and gel formation of pectin are very much dependent on the pH of surroundings. It is insoluble at an alkaline and neutral pH but soluble at acid condition. Upon dissolution, amine groups of the polymer become protonated, forming a resultant viscous and soluble polysaccharide.

Inclusion of citric acid as pH-regulating excipient in the developed formulations was expected to decrease the microenvironmental pH of the core to a suitable level at which pectin could form appropriate viscous gelling solution and hence, to enhance the osmotic pressure of core tablets.

In initial trials, core tablets were coated with microporous membrane (formulation code: P1S2). However, there was no drug release till 18 hr. It was probably because no gel forming action happened to pectin. Based on this, we thought that it was necessary to add a suitable amount of citric acid into core tablets in order to gelatinize pectin.

It was clearly evident from studies that the concentration of citric acid in the core formulation had a marked effect on drug release after it came with SCF. As the concentration of citric acid increased, viscosity of pectin solution also increased, which caused the increment of osmotic pressure of core tablets. It could be seen that release amount was higher in batch P3 (94.74%) compared with that in batch P2 (92.84%) and P1 (0%) where the concentrations of citric acid were lower. When the amount of citric acid added into the tablets increased, a greater amount of pectin would be gelled and hydrated, thus the osmotic pressure that pushed the drug suspension solution out of the system would increase accordingly. At the same time, we found as further increase of citric acid, there was no proportionate increase in drug release.

5.4.2.2. Effect of amount of pectin on drug release

Based on above result, the core formulation P3 (pectin/ citric acid ratio 1:2) was selected as

optimum for the following studies. However, the amount of drug release was not sufficient. To improve the amount of drug release, four different amounts (P3: 90 mg, P5: 99 mg and P6: 72 mg, respectively) of pectin–citric acid mixture (1:2) were taken in core tablets to observe the effect on drug release after 18 hr dissolution studies.

The influence of different added amounts of pectin–citric acid mixture (1:2) on the amount of drug release from osmotic core tablets with an in situ delivery pores formation was noted. P5 showed 92% drug release and P3 showed 95% drug release, indicating that decrease of pectin reduced the viscosity of core tablets and thus decreased the osmotic pressure. P4 (99.28%) showed considerable increment of drug release. As a suspending agent, the larger the amount of pectin being used, the higher the viscosity of the core suspension would be, leading to more efficient suspension of water-insoluble dexamethasone in the tablets. As a consequence, the release amount increased when increasing the added amount of pectin, because the available surface area for drug dissolution enhanced.

Hence, core formulation P4 was adopted in further formulation studies.

5.4.3. Evaluation of membrane variables

5.4.3.1. Effect of concentration of pore forming agent (pectin) on drug release

The SEM and further isolated film study have proved that pectin incorporated in CA films was susceptible to digestion by bacterial enzymes in a simulated colonic environment and allowed drug release to occur. The extent of digestion was directly proportional to the amount of pectin present in the film.

To study the effect of concentration of pore forming agent (pectin), core formulation F4 was coated with coating compositions containing 25% and 15%, w/w (of coated membrane weight) concentrations of pectin (P4S2 and P4S4, respectively). Release profiles from these formulations, in comparison with P4S3 (containing 20%, w/w of pectin) was recorded.

It clearly evidenced that the concentration of pectin had a direct effect on drug release. The formulation of coating composition S2 released more than 98% of dexamethasone after complete dissolution studies. This result suggested that slightly higher concentration of pore forming agent may be useful to release maximum dexamethasone content from the systems.

5.4.3.2. Effect of the concentration of enteric polymer of enteric-coating membrane on drug release

In all above release studies, the weight gain of 5% of enteric coating membrane was kept constant. Neither in situ formation of delivery pores nor drug release were observed before SCF dissolution studies. To study the effect of concentration of enteric polymer (Eudragit® L100-55), core formulation P4S2 was coated with coating compositions containing 8%, 6% and 4% w/w (of coated membrane weight) concentrations of Eudragit® L100-55. Release profiles from these formulations are shown in Fig. 4.14. It clearly indicated that the concentration of Eudragit® L100-55 had a direct effect on drug release. The formulation of coating composition E1 released more than 95% of dexamethasone after complete dissolution studies. This result suggested that slightly higher concentration of Eudragit® L100-55 may be useful to release maximum dexamethasone content from the systems.

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, matrix, peppas and Hix-Crowell) in order to describe the kinetics of drug release after in situ formation of delivery pores (i.e. after 6 h). The sum of squares of residues (SSR), regression analysis (R) and correlation coefficient (k) were taken as criteria for choosing the most appropriate model.[3] Drug release from optimal formulations fitted well into zero order model (and apparent lag time was 6 h. This experiment confirmed that pectin in the mixed film coat was accessible to enzymatic attack. The degradation of pectin was therefore a rate-limiting factor.

Table 4.2 Melting range

S. no.	Reported value[1]	Observed value
1.	262-264□C	261-264□C

Table 4.3: Qualitative solubility of drug in different solvents

S. No.	Solvents	Solubility
1.	Acetone	***
2.	Methanol	***
3.	Ethanol	***
4.	Buffer 6.8	**
5.	Buffer 7.4	**
6.	Distilled water	*

Table 4.4: Quantitative solubility of drug in different solvents

S. No.	Solvent	Absorbance	Concentration µg/ml
1.	Methanol	0.441	9.32
2.	Buffer 6.8	0.423	8.84
3.	Buffer 7.4	0.373	8.92
4.	Water	0.01	0.184

Table 4.6: Compatibility studies design.

S. no.	Partition coefficient (o/w)	
	Reported value[5]	Observed value
1	1.1	0.97

Table 4.7: **Interpretation of F.T.I.R. spectra of 1:1 mixture of drug and polymers**

S.No.	Sample	Ratio
1.	Dexamethasone (drug)	-
2.	Dexamethasone + Pectin	1:1
3.	Dexamethasone + Citric acid	1:1
4.	Dexamethasone + chitosan	1:1
5.	Dexamethasone + SMCC	1:1
6.	Dexamethasone + Eudragit® L100-55	1:1
7.	Dexamethasone + Cellulose acetate	1:1
8.	Dexamethasone + Pectin + Citric acid + Pectin + SMCC + Eudragit® L100-55 + Cellulose acetate	1:1

Table 4.8: - Standard curve of dexamethasone in water:

S. No.	Functional group	I.R Signals cm^{-1}	
		Pure drug	Drug + polymer
1.	**O-H stretching**	3430.32	3388.61
2.	**C-H stretching**	2930.38	2942.31
3.	**C=O stretching**	1717.93	1718.54
4.	**C-O stretching**	1384.13	1438.12
5.	**C-H deformation**	1271.39	1244.52
6.	**C-O stretching**	1105.49	1141.25
7.	**C-H deformation**	985.75	989.94

Table-4.9 Standard curve of dexamethasone in 0.1 N HCl

S. No.	Concentration (µg / ml)	Absorbance (242 nm)
1.	0.5	0.035
2.	1.0	0.055

3.	1.5	0.085
4.	2.0	0.112
5.	2.5	0.136
6.	3.0	0.165
7.	3.5	0.194
8.	4.0	0.224
9.	4.5	0.245
10.	5.0	0.271

Table 4.10: Standard curve of Dexamethasone in phosphate buffer solution pH 5.0

S. No.	Concentration (µg / ml)	Absorbance (242 nm)
1.	1	0.06
2.	2	0.099
3.	3	0.147
4.	4	0.202
5.	5	0.244
6.	6	0.302
7.	7	0.346
8.	8	0.403
9.	9	0.467
10.	10	0.501

Table 4.11: - Standard curve of dexamethasone buffer of pH – 6.8

S. No.	Concentration (µg / ml)	Absorbance
1.	1	0.015
2.	2	0.030
3.	3	0.047
4.	4	0.051
5.	5	0.068
6.	6	0.080
7.	7	0.090
8.	8	0.106
9.	9	0.113
10.	10	0.118

Table 4.12: - Standard curve of dexamethasone buffer of ph – 7.4

S. No.	Concentration (µg / ml)	Absorbance (242 nm)
1.	0	0
2.	1	0.041
3.	2	0.085
4.	4	0.177
5.	6	0.286
6.	8	0.370
7.	10	0.452

8.	12	0.557
9.	14	0.663
10.	16	0.742
11.	18	0.855
12.	20	0.962

Table 4.13: Composition for core tablets

S. No.	Concentration (µg / ml)	Absorbance (242 nm)
1.	1	0.033
2.	2	0.074
3.	4	0.164
4.	5	0.215
5.	6	0.265
6.	8	0.327
7.	10	0.419
8.	12	0.492
9.	14	0.592
10.	16	0.672
11.	18	0.747
12.	20	0.827

Table 4.14: Microporous semipermeable membrane coating formulations

S. No.	Ingredients (mg/tablet)	Core code				
		P1	P2	P3	P4	P5
1.	**Dexamethasone**	0.5	0.5	0.5	0.5	0.5
2.	**Pectin**	60	30	30	33	24
3.	**Citric acid**	0.0	30	60	66	48
4.	**SMCC**	54	54	24	15	42
5.	**Mag. stearate**	0.6	0.6	0.6	0.6	0.6

Table 4.15: Enteric coating formulation

S. No.	Formulation code	Coating composition (%)		
		Pectin	CA	TEC
1.	S1	30	45	25
2.	S2	25	50	25
3.	S3	20	55	25
4.	S4	15	60	25

Table 4.16: Physico-Chemical Characterization of core tablets of Dexamethasone

S. No.	Formulation code	Coating composition			
		Eudragit® L100-55 (gm)	I.P.A. (ml)	Acetone (ml)	TEC (ml)

1.	E1	8	73	42.2	1.5
2.	E2	6	73	44.7	1.5
3.	E3	4	73	47.1	1.5

Table 4.17: Physico-chemical characterization of microporous semipermeable membrane coated tablets

S. No.	Formulation Code	Uniformity of weight	Thickness (in mm)	Diameter (in mm)	Friability (%)	Hardness (kg/cm^2)
1.	P1	114.5±1.18	2.41±0.02	8.0±0.04	0.65 ± .05	10.02±0.15
2.	P2	114.6±1.08	2.49±0.03	8.0±0.03	0.75 ± .05	10.01±0.13
3.	P3	113.6.±1.57	2.40±0.4	8.1±0.08	0.69±0.05	8.05±0.081
4.	P4	114.4±1.05	2.48±0.03	8.0±0.04	0.57±0.02	8.02±0.132
5.	P5	114.0±1.23	2.42±0.02	8.02±0.05	0.53±0.03	10.3±0.12

Table 4.18: Physico-chemical characterization of tablets coated with enteric coating

S.No.	Formulation Code	Uniformity of weight (in mg)	Thickness of tablet (mm)	Diameter of tablet (mm)
1.	P1S2	128.3±0.345	2.70±0.02	8.51±0.05
2.	P2S2	128.4±0.832	2.68±0.03	8.42±0.03
3.	P3S2	127.2±0.563	2..73±0.03	8.53±0.04
4.	P4S2	128.25±0.842	2.71±0.07	8.52±0.04
5.	P5S2	127.7±0.848	2.74±0.06	8.50±0.05
6.	P4S1	129.23±0.523	2.65±0.05	8.32±0.07
7.	P4S2	128.25±0.842	2.71±0.07	8.52±0.04
8.	P4S3	130.12±0.944	2.63±0.06	8.21±0.06
9.	P4S4	128.05±0.872	2.72±0.08	8.52±0.08

Table 4.19: Cumulative % drug release from various formulations showing effect of diluents, polymer and the ratio of pectin and citric acid

S.No.	Formulation Code	Uniformity of weight (in mg)	Thickness (in mm)	Drug content (%)
1.	P4S2E1	134.778±0.672	2.82±0.05	99.02±0.03
2.	P4S2E2	136.068±0.864	2.80±0.08	98.23±0.04
3.	P4S2E3	135.921±0.946	2.83±0.05	98.05±0.07

Table 4.20: Cumulative % drug release from various formulations showing effect of concentration of pore forming agent

S. No.	Time (hr)	Cumulative % drug release from different formulations			
		P2S2	P3S2	P4S2	P5S2
1.	1	7.107±2.76	5.832±0.55	5.991±0.48	11.575±3.08
2.	2	11.965±2.79	10.837±0.48	11.317±0.47	19.988±4.81

3.	4	23.253±2.71	20.406±0.31	21.482±0.48	29.920±0.27
4.	6	29.866±4.76	32.847±0.56	33.821±0.55	35.003±0.27
5.	8	38.139±2.78	43.383±0.74	45.325±0.28	42.527±2.23
6.	10	44.895±0.05	54.501±0.02	57.578±0.73	48.208±2.72
7.	12	51.716±2.72	65.885±1.01	68.992±0.96	55.218±4.84
8.	14	74.556±2.30	76.420±1.23	80.675±0.83	74.899±4.69
9.	16	83.259±5.56	85.458±0.24	90.871±0.72	87.591±2.51
10.	18	91.040±2.42	95.001±0.69	99.247±0.54	92.020±1.39

Table 4.21: Cumulative % drug release from various formulations showing effect of concentration of enteric polymer:

S. No.	Time (hr)	Cumulative % drug release from various formulations			
		P4S1	**P4S2**	**P4S3**	**P4S4**
1.	1	12.091±0.342	5.991±0.48	6.853±0.05	5.671±0.28
2.	2	25.098±0.543	11.317±0.47	7.193±0.07	11.951±2.76
3.	4	58.987±0.374	21.482±0.48	13.950±0.28	20.048±4.78
4.	6	80.098±0.623	33.821±0.55	33.235±0.27	25.033±4.83
5.	8	99.094±0.7243	45.325±0.28	60.690±0.48	38.045±2.86
6.	10	-	57.578±0.73	67.194±0.28	43.365±2.61
7.	12	-	68.992±0.96	72.960±0.49	49.852±0.42
8.	14	-	80.675±0.83	83.244±0.84	71.239±2.32
9.	16	-	90.871±0.72	86.604±1.52	83.101±3.23
10.	18	-	99.247±0.54	94.457±0.47	91.086±1.19

Table 4.22: Regression analysis, correlation coefficient and sum of squares of residual values for drug release data of optimized formulations according to various mathematical models:

S. No.	Time (hr)	Cumulative % drug release from various formulations		
		P4S2E1	**P4S2E2**	**P4S2E3**
1.	1	-	-	-
2.	2	-	-	-
3.	4	-	-	-
4.	6	5.832±0.28	6.231±0.05	7.107±2.76
5.	8	10.996±0.73	7.193±0.07	11.951±2.79
6.	10	21.158±0.73	13.950±0.28	23.253±2.71
7.	12	32.537±0.54	33.235±0.27	29.866±4.76
8.	14	41.794±0.28	60.690±0.48	38.139±2.78
9.	16	55.129±0.28	67.194±0.28	44.895±0.05
10.	18	63.488±0.56	72.960±0.49	51.716±2.72
11.	20	75.594±0.29	83.244±0.84	74.556±2.31
12.	22	85.901±0.29	86.604±1.52	83.259±5.56
13.	24	95.027±0.47	93.456±0.47	92.840±2.42

Models	Parameters used to assess the fit of models	formulations		
		P4S2E1	P4S2E2	P4S2E3
Zero order	R	0.9996	0.9788	0.9880
	k	5.3448	5.7500	5.0175
	SSR	7	547	156
First order	R	0.9117	0.9583	0.8951
	k	-0.1168	-0.1288	-0.1045
	SSR	1469	1476	1658
Matrix	R	0.9335	0.9287	0.9174
	k	18.5218	20.0203	17.3469
	SSR	1383	1797	1498
Peppas	R	0.9995	0.9707	0.9872
	k	5.6584	4.8616	6.5536
	SSR	7	633	235
Hix- Crowell	R	0.9644	0.9831	0.9422
	k	-0.0285	-0.0313	-0.0261
	SSR	568	680	822

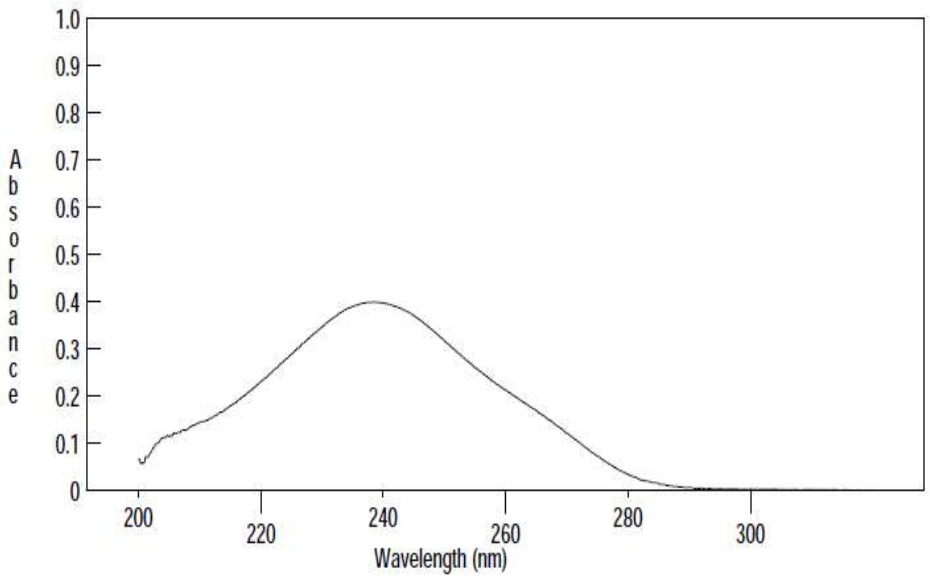

Figure 4.1: **UV Scanning Curve of reference dexamethasone (10µg/ml) pure drug.**[3]

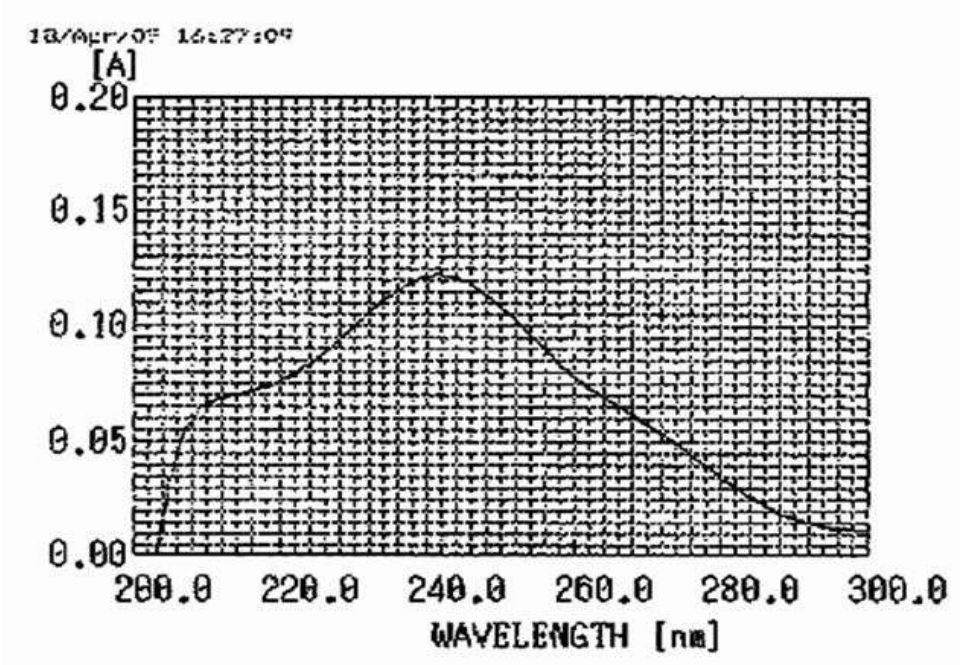

Figure 4.2: **UV Scanning Curve of sample dexamethasone (10 µg /ml) drug.**

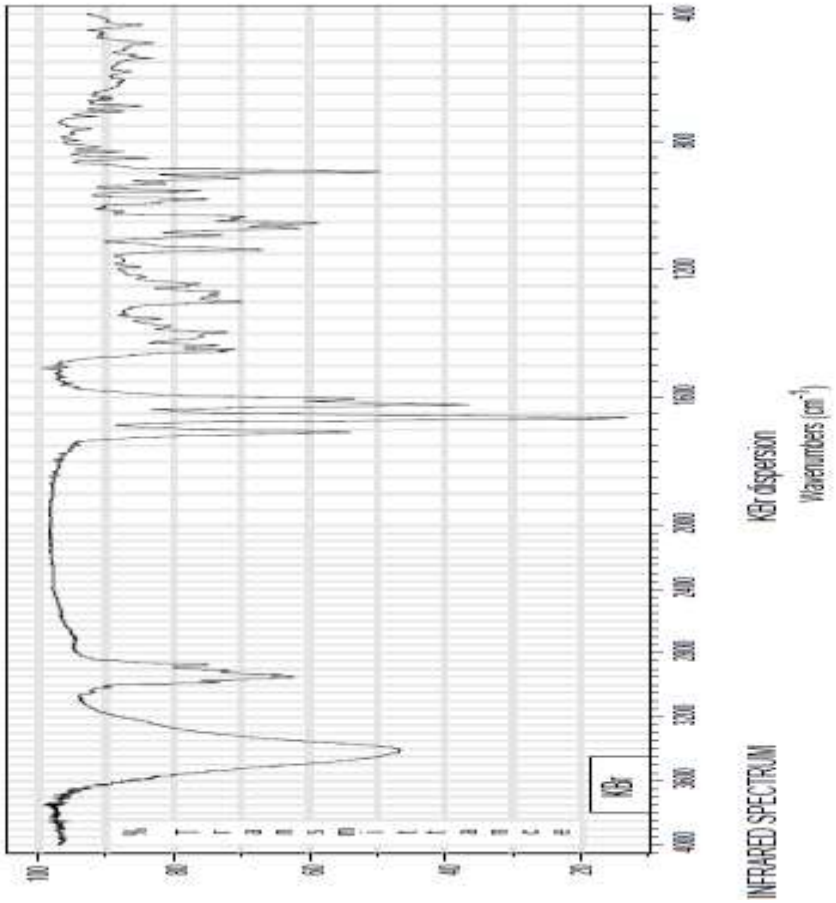

Fig: 4.3: F.T.I.R. spectra of reference dexamethasone pure drug[4]

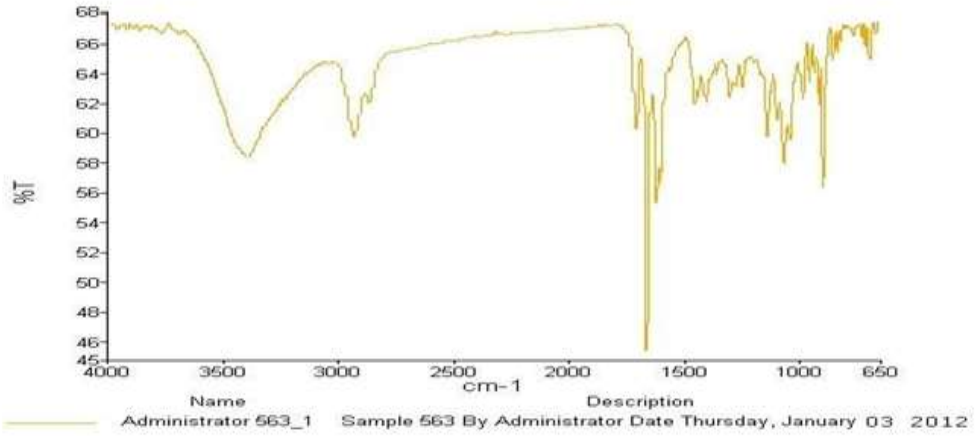

Fig: 4.4: F.T.I.R. spectra of sample dexamethasone drug

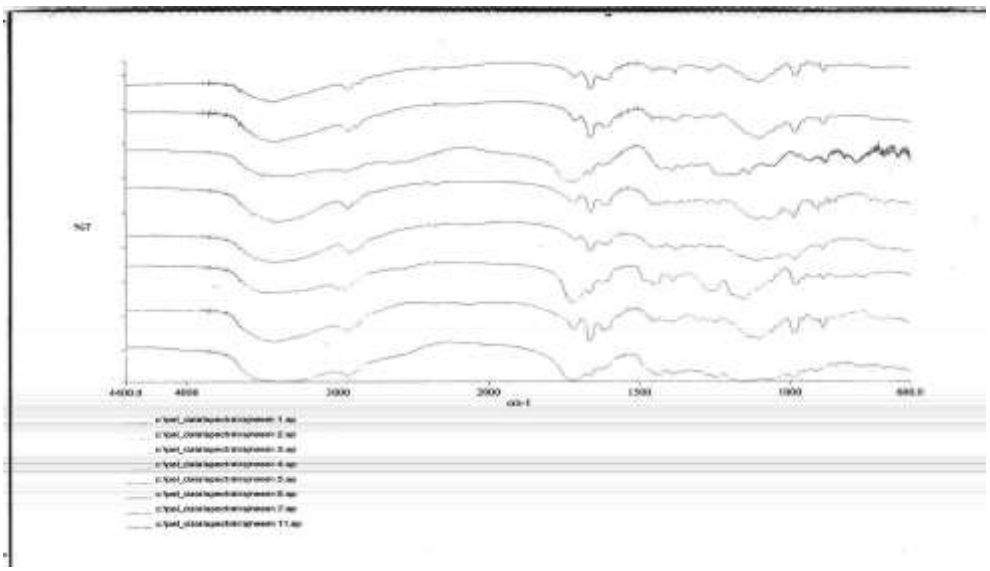

Figure 4.5: F.T.I.R. Spectra showing compatibility of drug with polymer.

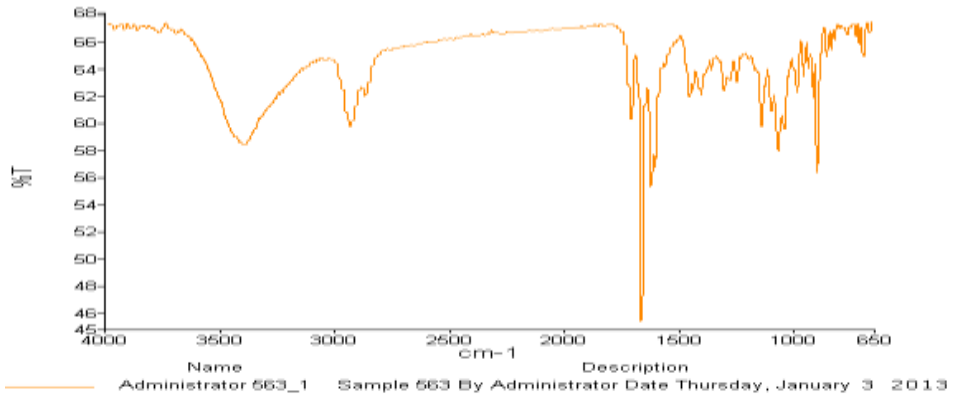

Figure 4.6: F.T.I.R. Spectra showing compatibility of drug with polymer.

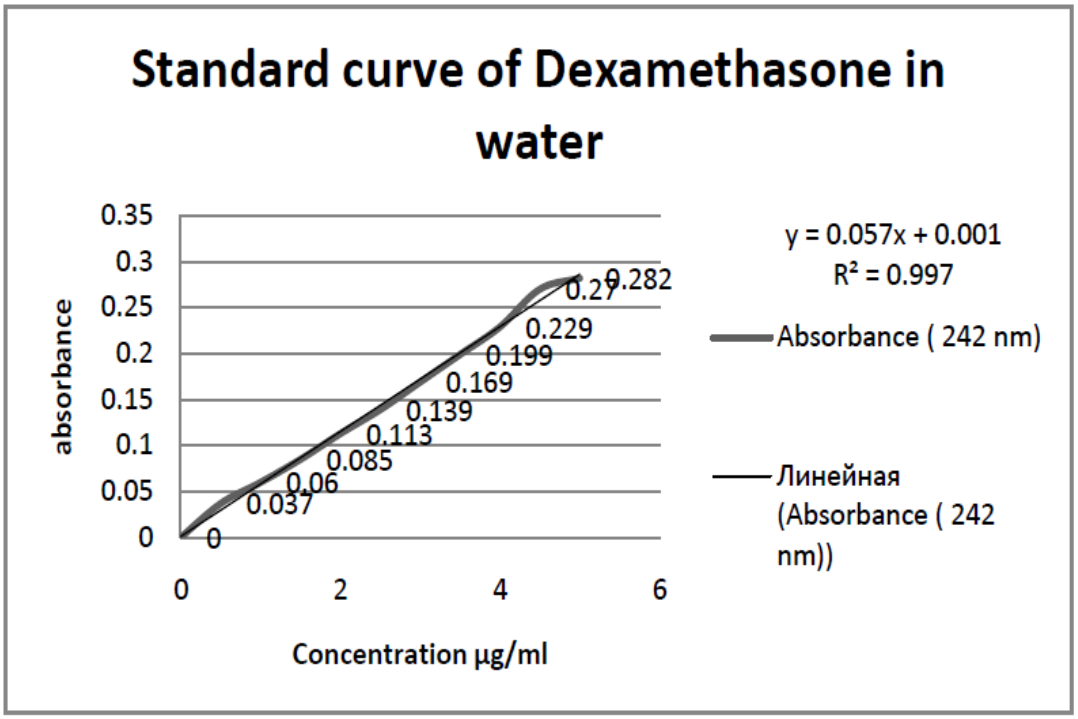

Figure 4.7: Standard curve of dexamethasone in water (242 nm)

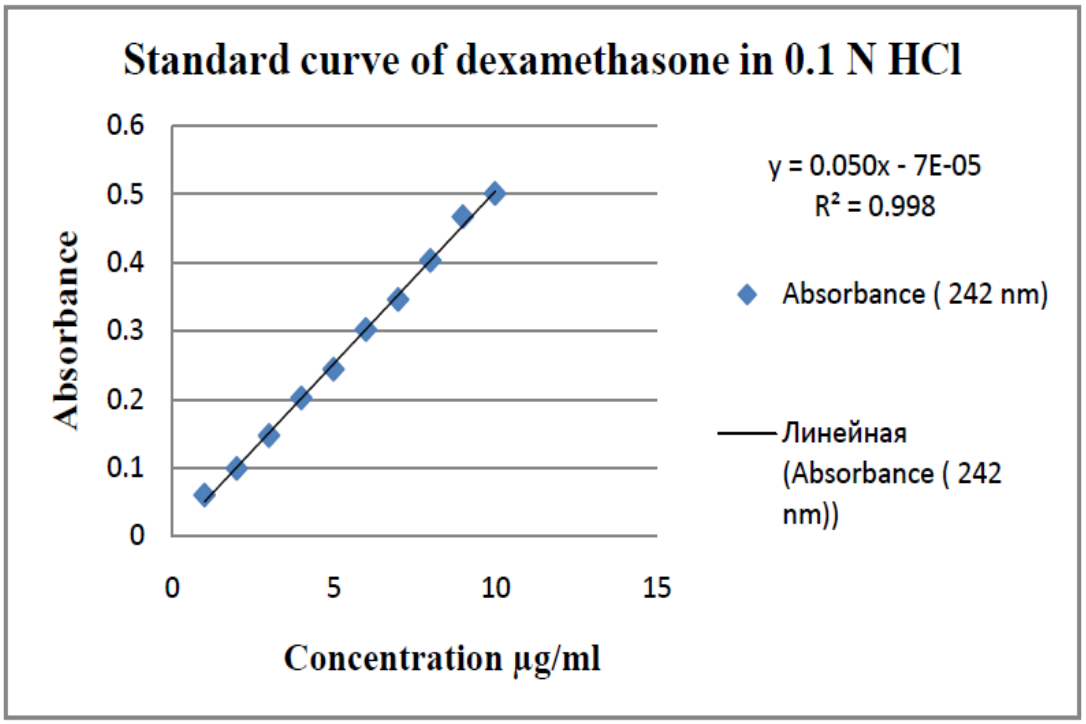

Figure 4.8: Standard curve of dexamethasone in 0.1 N HCL (242 nm)

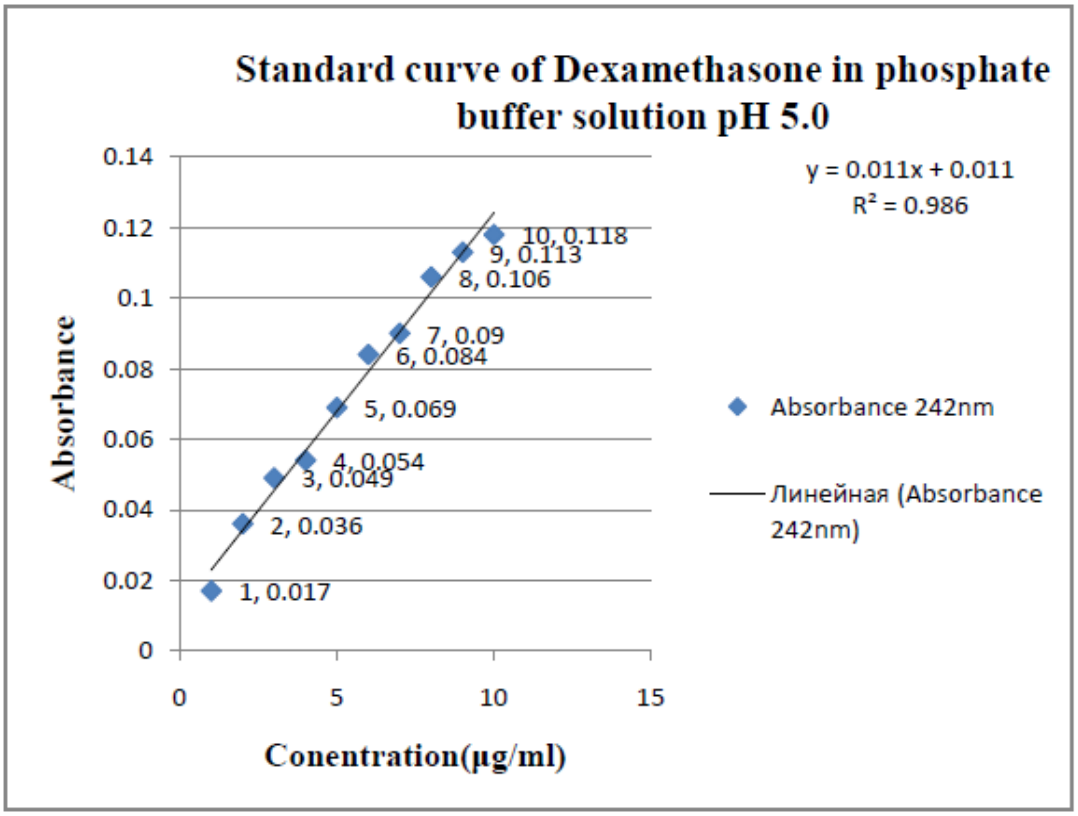

Figure 4.9: Standard curve of dexamethasone in buffer pH 5.0 (242 nm)

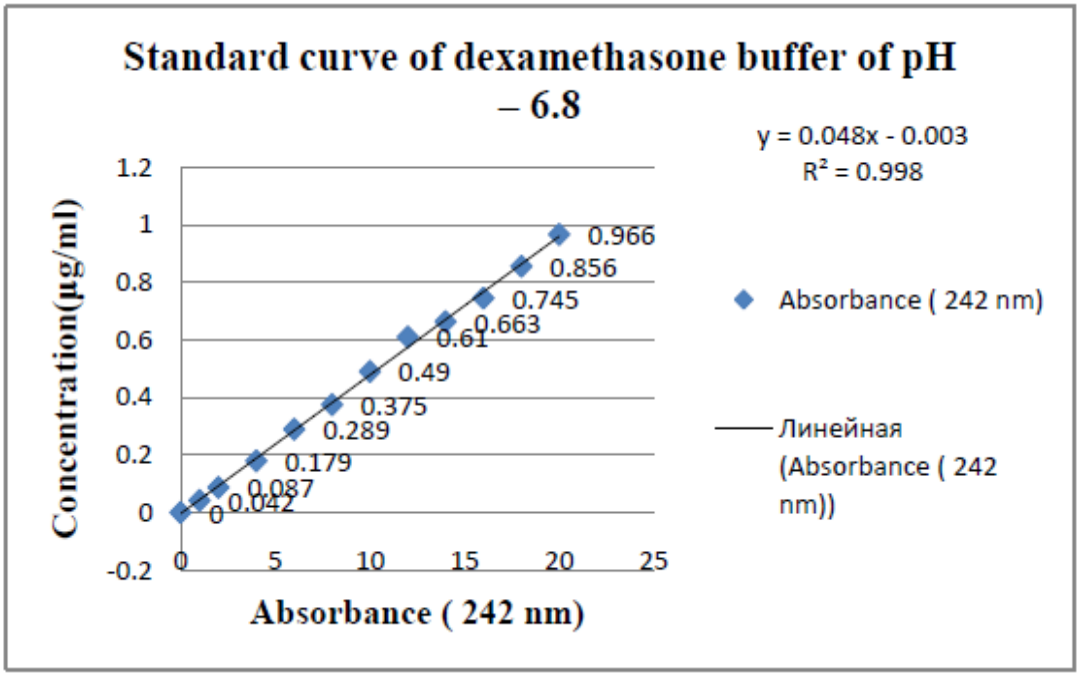

Figure 4.10: Standard curve of dexamethasone in buffer pH 6.8 (242 nm)

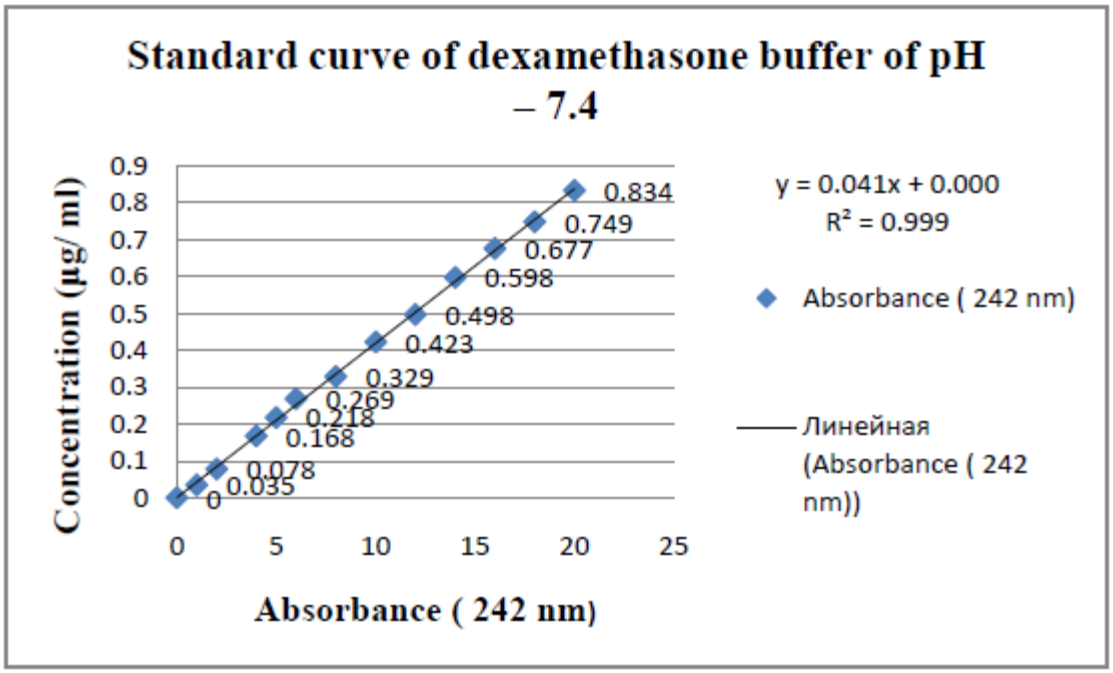

Figure 4.11: Standard curve of dexamethasone in buffer pH 7.4 (242 nm)

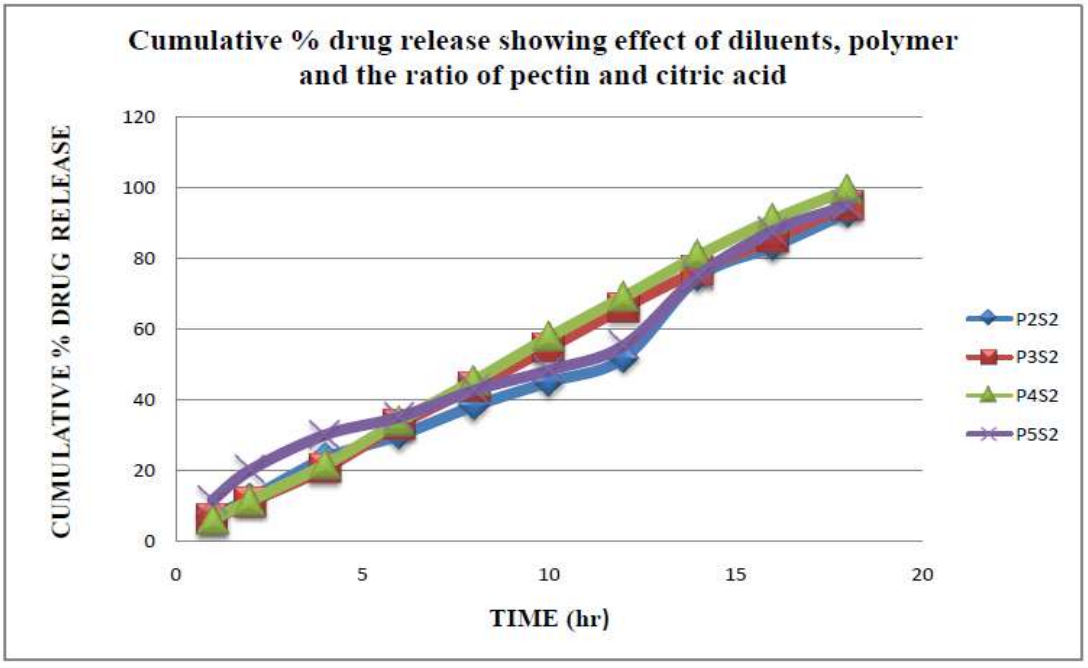

Figure 4.12: Effect of diluents, polymer and the ratio of pectin and citric acid on release of drug

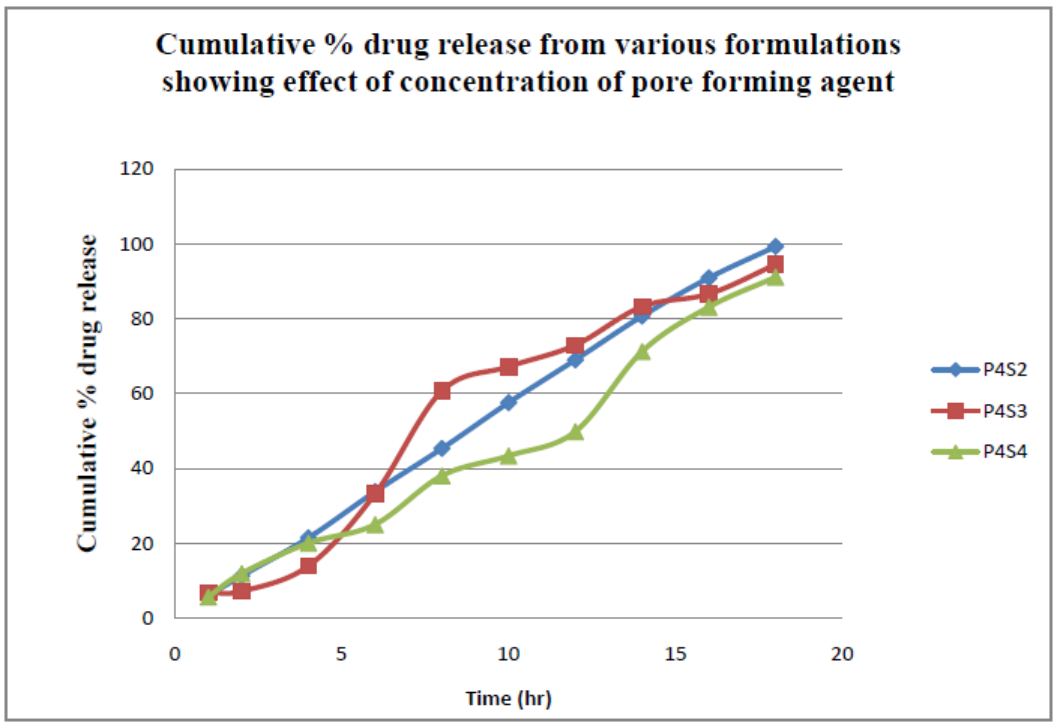

Figure 4.13: Effect of concentration of pore former

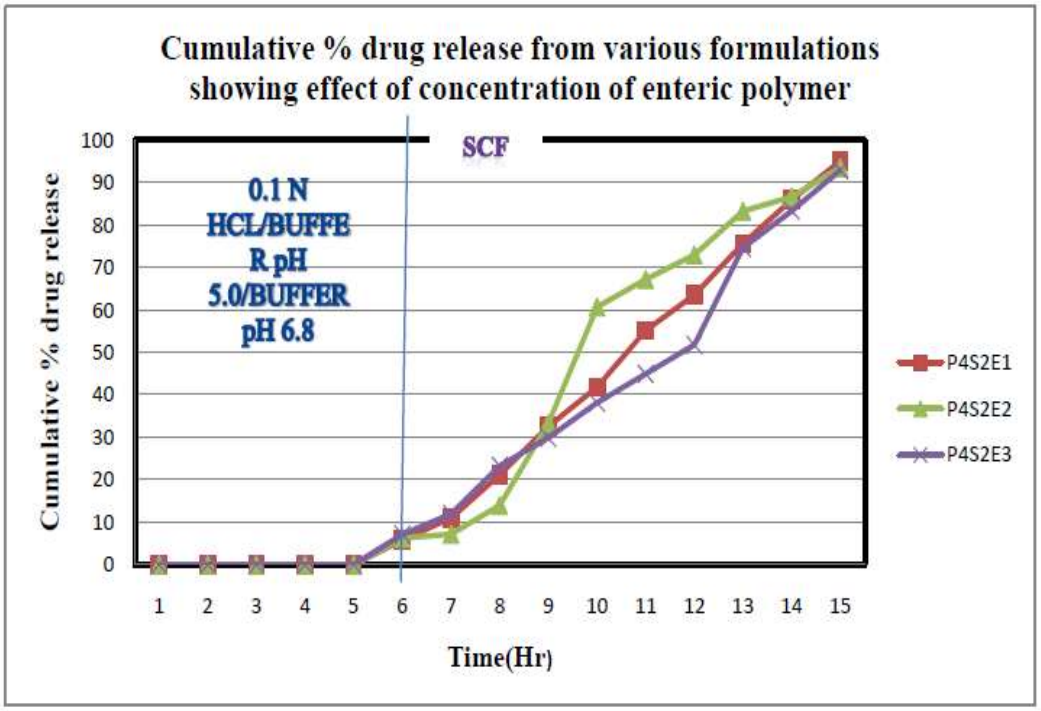

Figure 4.14: Effect of concentration enteric polymer on drug release

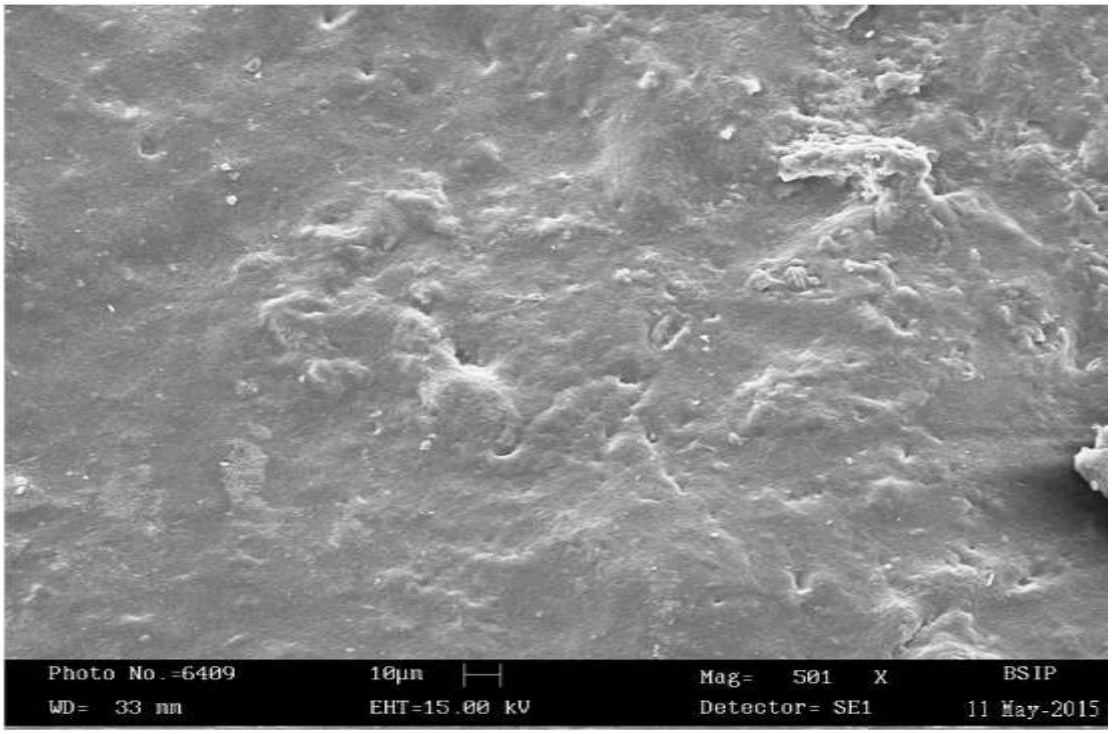

Figure 4.15: SEM of formulation P4S2 before dissolution.

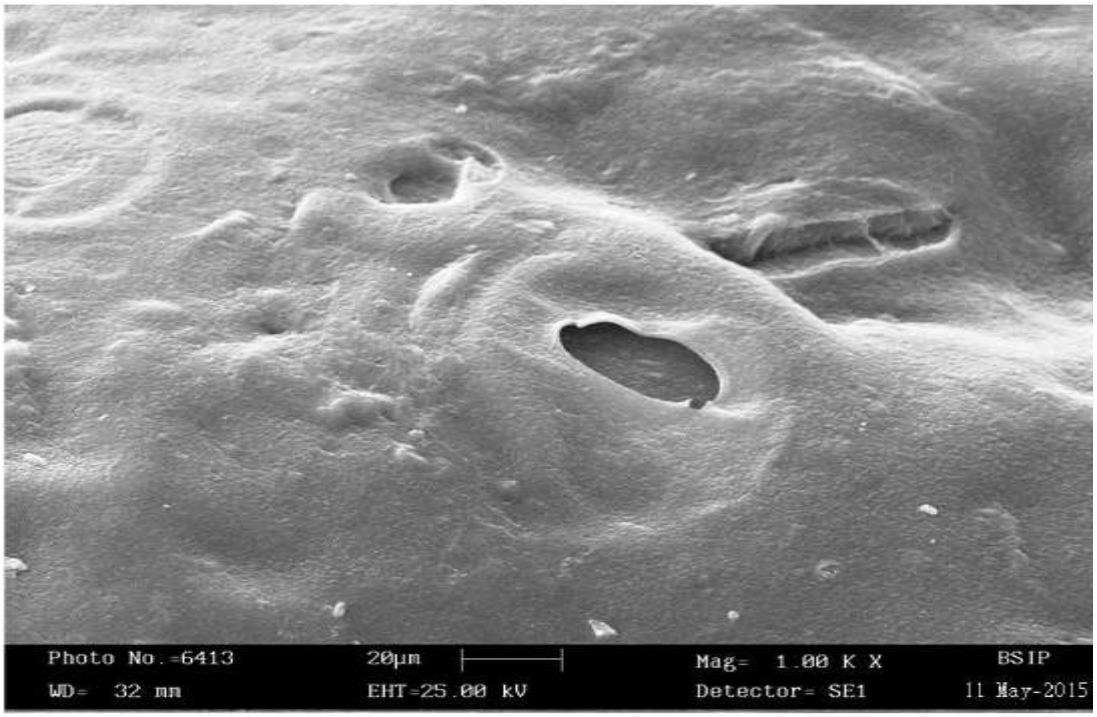

Figure 4.16: SEM of formulation P4S2 after dissolution.

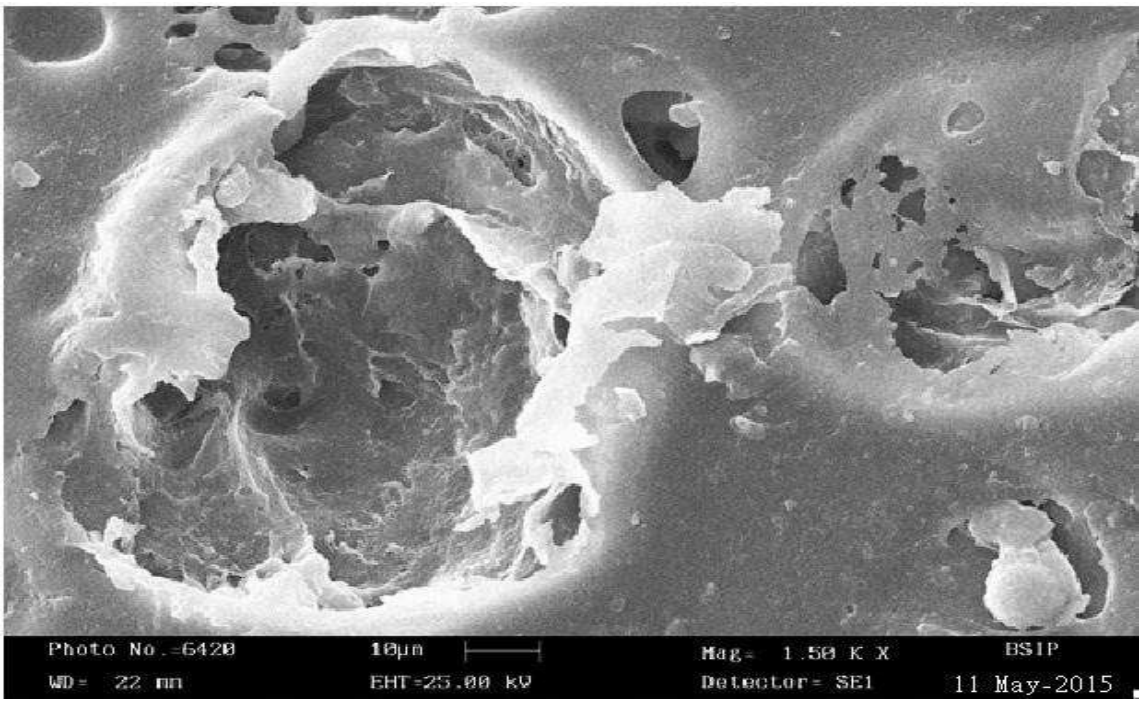

Figure 4.17: SEM of formulation P4S2E1 before dissolution.

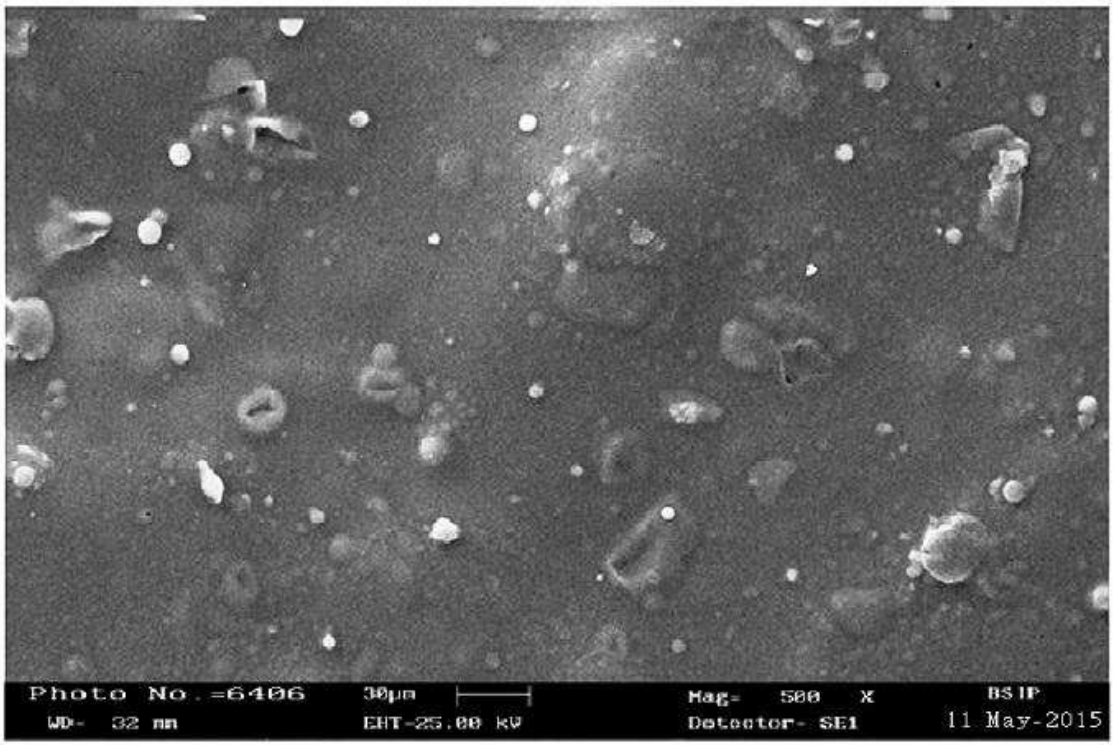

Figure 4.18: SEM of formulation P4S2E1 after dissolution.

Kinetics of drug release

In general the release of drug from an osmotic system depends on many factors such as osmotic pressure, pore size and coating thickness. In order to describe the kinetics of drug

release from P4S2E1, P4S2E2 and P4S2E3 formulations, various mathematical equations have been proposed. The zero-order rate (Equation 1) describes systems where drug release is independent of its concentration and is generally seen for poorly water soluble drug in matrix, transdermals, etc. The first-order equation (Equation 2) describes systems in which the release is dependent on its concentration (generally seen for water-soluble drugs in porous matrix). The Hixson- Crowell cube root law (Equation 3) describes the release of drug from systems where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in the case of systems that dissolute dissolute or erode over time. In order to authenticate the release model, dissolution data can further be analyzed by Peppas and Korsmeyer (Equation 4).

$Q_t = k_0 t$ ..... (1)

$\ln Q_t = \ln Q_0 - k_1 t$ ..... (2)

$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t$ ..... (3)

$\frac{M_t}{M_\infty} = kt^n$ ..... (4)

Where Q_t is the amount of drug released at time t; Q_0 is the initial amount of the drug in the formulation; k_0, k_1, k_H and k_{HC} are release rate constants for zero-order, first-order, Higuchi model and Hixson-Crowell rate equations. In Equation 10, M_t is the amount of drug released at time t and M_∞ is the amount released at time ∞; k is the kinetic constant and n is the diffusional coefficient. The criteria for the best model were based on goodness of fit and sum of squares of residual (SSR)[11]

Table 4.22: Regression analysis, correlation coefficient and sum of squares of residual values for drug release data of optimized formulations according to various mathematical models:

Models	Parameters used to assess the fit of models	formulations		
		P4S2E1	P4S2E2	P4S2E3
Zero order	R	0.9996	0.9788	0.9880
	k	5.3448	5.7500	5.0175
	SSR	7	547	156
First order	R	0.9117	0.9583	0.8951
	k	-0.1168	-0.1288	-0.1045
	SSR	1469	1476	1658
Matrix	R	0.9335	0.9287	0.9174
	k	18.5218	20.0203	17.3469

	SSR	**1383**	**1797**	**1498**
Peppas	**R**	**0.9995**	**0.9707**	**0.9872**
	k	**5.6584**	**4.8616**	**6.5536**
	SSR	**7**	**633**	**235**
Hix- Crowell	**R**	**0.9644**	**0.9831**	**0.9422**
	k	**-0.0285**	**-0.0313**	**-0.0261**
	SSR	**568**	**680**	**822**

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