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Research Article

FORMULATION AND EVALUATION OF DUAL-LAYERED OSMOTIC PUMP CONTROLLED-RELEASE TABLETS OF CEFIXIME

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ABSTRACT

Background: This study aims to formulate, optimize and evaluate the osmotic tablet of cefixime. It improves the site specification and provides the controlled release of drug once – a – day through this drug delivery system. Cefixime assumes a significant part in dissolvability restricts other than dissolvable sort. It might increase the bioavailability of drugs by the preparation of the osmotic tablet. Method: The forming core tablet does a formulation of Controlled Porosity Osmotic Tablets (CP1 – CP9) using an ingredient like sodium chloride, PVP K30, Microcrystalline cellulose various ratios. The coating of the core tablet is done by Cellulose Acetate, PEG 400, with statistical ratios. Result: On depending upon the various evaluation parameters like hardness, diameter, friability, weight variation, content uniformity, In vitro release, CP9 formulation gave better consequence. The percentage of drug release is >95%. The optimized CP9 batch showed a maximum correlation of 0.992 with a zero-order drug release kinetic model. Conclusion: A controlled release formulation of cefixime based on osmotic technology, were developed. The release from the developed formulation was independent of pH and agitational intensity of the release media; the formulation fitted well into zero-order kinetics, indicating the release to be drug load independent. Drug release was directly proportional to the initial pore level but inversely related to the membrane weight. The release was inversely associated with the release media's osmotic pressure, confirming osmotic pumping as the central mechanism of release.

Keywords: Osmotic drug delivery system, bioavailability, evaluation parameter, zero-order

INTRODUCTION

Cefixime is measured as a significant and energetic member of a third-generation cephalosporin. The cefixime exists in off white crystals, melts over 220-250˚C and soluble in alcohol. Orally active cefixime has outstanding activity against anaerobes, enterobacteria, gram-negative species such as Escherichia coli, haemophilus, branhamella catarrhalis, neisseria gonorrhoeae. The absolute oral bioavailability of cefixime is in the range of 22-54%. Protein binding of cefixime depends on human serum only at a very high concentration which is not seen following clinical dosing. The area under the time versus concentration curve is superior by about 26.4%, and the C_{max} is bigger by around 20.7%. Cefixime is used to treat bacterial infections includes otitis media, pneumonia, strep throat, urinary tract infections, gonorrhoea and lyme disease.

Cefixime was approved in the USA in 1989. It is marketed under many trade names such as text (Apex, Lef-3 and Denvar). Cefixime chemical formula is $C_{16}H_{15}N_5O_7S_2$, and molecular mass is 453.452 g/mol.

Literature survey reveals that there are only a few spectrometric methods available for the determination of drug. THE reported U.V. method has used a specific model that is only available in sophisticated instruments.

The present study aimed to develop a simple, sensitive, accurate, versatile, and fast UV method to estimate cefixime. The projected methods were validated in compliance with ICH guidelines and were magnificently applied to determine cefixime in their pharmaceutical formulation.

The National Coordination Centre (NCC) – Pharmacovigilance Programme of India (PvPI), Indian Pharmacopoeia Commission (IPC), has received rare individual case safety reports (ICSRs) for acute generalized exanthematous (AGEP) associated with the use of cefixime.

Determination of cefixime was reported in literature survey by many of different analytical techniques such as UV, FTIR and DSC. [1-2]

MATERIALS AND METHOD

Chemicals and reagents

Cefixime was produced by the Sherincorps Solutions Inc. Sodium chloride, MCC, SLS, Magnesium stearate, talc, cellulose acetate and PEG 400 from CDH laboratories. Povidone K30 from Qualikens laboratory and Acetone from Finar laboratory.

Solubility Test: - Standard stock solution of cefixime was performed by using solvent methanol.

Determination of λmax: - Preparation of stock solution
The standard stock solution of cefixime was equipped by dissolving 10mg of cefixime in 10ml of methanol which gives 1000µg/ml. 1ml of the stock solution was taken and diluted up to 10ml by using methanol to produce a concentration of 100µg/ml solution.

Preparation of working solution
From directly above stock solution, 1ml transferred into a 10ml volumetric flask and volume was made up to the mark with

methanol to make 10µg/ml. Then the sample was perused with UV- visible spectrophotometer in the range 200-400 nm against 0.1N, and the wavelength conforming to maximum absorbance was noted at 286 nm, respectively.

Preparation of calibration curve in methanol
From the above stock solution (100µg/ml), further dilution was made, and the volume was made up to 10ml using methanol to produce 10 µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml and 60µg/ml solution respectively.

Preparation of calibration curve in a phosphate buffer solution of pH 6.8

Preparation of phosphate buffer solution of pH 6.8: 11.45 gm of potassium dihydrogen phosphate (KH_2PO_4) was liquefied in some amount of distilled water then to this, 28.8 gm of disodium hydrogen phosphate (NA_2HPO_4) was added, and the volume was made up to 1000 ml with distilled water.

Preparation of standard solution of cefixime in PBS of pH 6.8: A standard solution was prepared by weighing accurately 10 mg of cefixime in 100 ml volumetric flask, and volume was made up to 100 ml with freshly prepared buffer to give a concentration of 100µg/ml (stock solution).

Dilution: Procedure: From the stock solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 ml, volumes were pipette out in 10 ml volumetric flask separately and volume made up with buffer to give 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 µg/ml of concentration respectively. The stock solution was perused over the range of 200-400 nm, spectrum mode in a U.V. visible spectrophotometer. A calibration curve was plotted between concentration and absorbance.

Preparation of calibration curve in a phosphate buffer solution of pH 7.4

Preparation of phosphate buffer solution of pH 7.4: 0.19 gm of potassium dihydrogen phosphate and 8 gm NaCl was dissolved in some amount of distilled water, then 2.38 gm of disodium hydrogen phosphate was added to it and capacity was made up to 1000 ml with distilled water

Preparation of standard solution of cefixime in PBS of pH 7.4: Stock solution of cefixime(100 µg/ml) was prepared. Aliquots from this stock solution were pipette out into a 10 ml volumetric flask and diluted with phosphate buffer (pH 7.4) to get final concentrations in the range of 10-60 µg/ml. The absorbance values of the resultant solutions were measured using a UV spectrophotometer.

Dilution

Procedure: From the stock solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 ml, volumes were pipette out in 10 ml volumetric flask and volume was made up with buffer to give 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 µg/ml concentration respectively. The stock solution was perused over the range of 200-400 nm, spectrum mode in a U.V. visible spectrophotometer. The calibration curve was plotted between concentration and absorbance.

By I.R. Absorption Spectroscopy

Infra-red absorption spectroscopy (I.R.) measurements were performed using Perkin Elmer, FT-IR spectrophotometer using the KBr disc method. [3-4]

FORMULATION OF CONTROLLED POROSITY OSMOTIC PUMP (CPOP) [5-6]

To hinder the requirement for confounded laser drilling, tablets covered with controlled porosity layers have been described. These layers comprise a leachable material that breaks up upon contact with water, abandoning the pores through which the medication arrangement is pumped out. The creation of the CPOP system includes the pressure of centre tablets, covering the centres with a semi-permeable film with some water solvent specialist, which gets broken down when accompanying the equivalent. The details of the strategies utilized are as per the following.

Preparation of Core Tablets

Utilizing wet granulation strategy, tablet centre were compressed with a solitary station tablet press outfitted with 12mm and 14mm profound inward punches using wet granulation strategy. Diverse detailing of the centre tablets utilized in the current examination and the fixings there under-recorded.

Precisely weighed of every fixing was gone through sieve # 85. All ingredients aside from magnesium stearate, powder and povidone K30 were physically mixed in mortar in mathematical dilution. The dry mix was granulated with an adequate PVP K30 which was broken down in isopropyl alcohol. The powder mass was dried at 60˚C in a hot air stove for 6 hrs and went through sieve no. 20. This blend was punched with the assistance of a single station punching machine (HICON) to give a tablet of the hardness of around 4 kg/cm^2, which were tested with a Pfizer hardness analyzer.

Coating of CPOP Tablets

Coating action was performed on a 15 g batch of tablets in a regular coating pan (HICON). The container speed was kept steady, and the arrangement was physically sprayed onto the tablet bed with a coating gun. The manual covering system depended on discontinuous splashing and method. The tablet was put in the covering container; while the dish was turning, hot air was blown into it onto the tablet bed surface.

The tablet bed was preheated before applying the coating solution. The tablet was sprayed for a short time frame and followed by tumbling off a few seconds. The splash on and off-cycle proceeded for a few minutes. The tablets were dried in warm air. This entire technique has rolled till the ideal tablet weight was gotten. The tablets were additionally dried for around 12-15 hrs at a temperature of about 40˚C.

EVALUATION OF COATED TABLETS

The coated tablets were evaluated for the following parameters:

- Hardness
- Diameter
- Friability
- Weight variation
- Content uniformity
- In vitro release

Hardness
The strength of the covered tablet is expressed as tensile strength (kg/cm2). The tablet crushing load, which is the power needed to break a tablet into pieces by pressure. It was estimated utilizing a tablet hardness analyzer (Monsanto hardness analyzer).

Diameter
The diameter of ten randomly selected coated tablets was measured using a screw gauge.

Friability
The friability of coated tablets was controlled by utilizing Roche friabilator. It is expressed in percentage (%). 10 tablets were at first gauged (Wintial) and moved into friabilator. The friabilator was worked at 25 rpm for 4 minutes or approach 100 rpm. The tablets were weighed once more (Wfinal). The % friability was then determined by

$$\% \text{ Friability} = (1 - \text{Wfinal} / \text{Winitial}) \times 100$$

Weight Gain
To assess the weight of the tablet coating. Ten tablets were randomly taken from each group, and their weight in the wake of the coating was resolved. Percentage weight picks up was kept consistent to 3%.

Drug Content
To assess a tablet potential for viability, the drug per tablet should be checked from tablet to tablet and cluster to group. To carry out the test, 10 tablets were crushed utilizing mortar pestle. Amount comparable to 100 mg of drug was dissolved in 100ml phosphate buffer pH 6.8, separated and weakened up to 50µg/ml, and examined spectrophotometrically at 275 nm.

IN-VITRO DRUG RELEASE PROFILE [7-8]

The various details were evaluated for their In vitro drug release profile in phosphate buffer pH 7.4 (900 ml) utilizing USP II (paddle type) disintegration rate mechanical assembly. The mixing rate was 50 rpm, and the temperature was kept up at 37±0.5˚C. The coated tablets were dried around 24 hours before conduction the disintegration contemplates. At time zero, the tablets were dropped into the disintegration media. Standard rules were followed during the disintegration testing. Tests (5 ml) were removed at standard spans with the same assistance sampler. Afterwards, an equivalent volume of new media was put presented with the assistance of the same sampler into the disintegration compartment. A U.V. spectrophotometer then examined the samples at λmax 275nm.

The general condition for In vitro dissolution studies is summarized below.

Based on In vitro drug release batch, CP9 was selected for future evaluation such as
- Drug release as a function of weight gain
- Drug release as a function of external osmotic pressure
- Drug release as a function of pore former concentration
- Drug release as a function of agitation intensity

Drug Release as a Function of Weight Gain after Coating
The tablets were weighed when coated, and afterwards, the In vitro drug release was read for the coated tablets with the assistance of USP II disintegration mechanical assembly (paddle type). Tablets from the CP9 batch were coated to put on weight up to 6% and 8%. In vitro drug release was then contrasted and that of 3% weight gain to see the impact of last on medication discharge.

Drug Release as a Function of External Osmotic Pressure
The tablets were evaluated for their In vitro drug release profile in the presence of outer osmotic weight. This weight was made by adding 2% and 5% w/v of NaCl in the disintegration media. The remainders of the conditions were kept the same.

Drug Release As A function Of Pore Former Concentration
The effect of the concentration of pore former on the drug release from the enhanced formulation was investigated.

Drug Release as a Function of Agitation Intensity
Drug release from the osmotic pump, to an enormous degree, is free of the agitational force of the delivery media. Further, the impact of agitational power on the medication discharge from the enhanced detailing was examined.

KINETICS OF DRUG RELEASE FOR CPP9 BATCH [9-10]

The mathematical description of the whole drug release measure is somewhat troublesome in light of the no. of essential qualities that must be considered. Each model makes certain presumption, and because of these suspicions, the applicability of the separate models is limited to the specific drug-polymer system.

It was seen that the optimized "CP9" batch showed a maximum correlation of 0.992 with a zero-order drug release kinetic model.

RESULT & DISCUSSION

Preformulation Studies
Organoleptic properties of the drug were studied and complied with B.P (British Pharmacopoeia) specification.

Identification of the Drug

By IR Spectroscopy
The spectrum obtained was compared with the ranges of cefixime given in IP.
The peaks obtained depicted in fig. 12, and the characteristics of peaks clearly identify that the drug produced is cefixime.

By melting Point Determination
The melting point was found to be 218˚C - 225˚C. This complies with the BP value.

By UV Visible Spectrometry
Scanning was done in methanol, phosphate buffer pH of 6.8 and 7.4 and then calibration curve was prepared and as depicted in fig. 11, 12, 13, the linear relationship was found between absorbance and concentration of different dilution of the drug. Hence it showed that the drug followed beer lambert law so that U.V. spectrophotometry can be applied to the analysis of the drug.

Evaluation Parameter of Optimized Batch

Drug Content
The drug content of various batches was calculated and was found to be within limits per I.P. standards. For batch CP9, it was estimated to be 99.45±0.66.

In Vitro Drug Release Profile of Different Batches
All the prepared batches were tested for their in vitro drug release. It was observed that the % total drug release increases significantly as the concentration of osmogent is increased. Batch CP9 gave a % total drug release of 96.2476%.

In Vitro Drug Release as a Function of Percentage Gain in Weight
The batch of CP9 was evaluated for different % gain in weight after coating. It was observed that the % total drug release decrease as the % gain in the weight increase.

About 8% weight gain allowed 47.2824%, whereas 6% weight gain allowed 52.2068% of total drug release. The % gain in

weight of about 3% gave the desired release profile of 71.7689% in 12 hrs.

In vitro Release as A Function of external Osmotic pressure

To confirm that the drug release is osmotically driven, dissolution tests were carried out in media having two different concentration of sodium chloride, 2% and 5% W/V of the media. It was observed that the drug release decreases with increased external osmotic pressure with 2% NaCl in media tablet showed about 54.2800% drug release and with 5% NaCl in media it was showed about 48.4821%. This result gives an idea that the primary mechanism of drug release is osmotic.

In Vitro drug Release as A Function of Pore Former Concentration

It was observed that the drug release increased with the increase in the level of pore former with a concentration of 40% of former pore tablets shows about 71.7689% of drug release. With the concentration of 50% of pore former, it was revealed about 92.2068% drug release within 12 hrs.

Drug Release as a Function of Agitation Intensity

To a large extent, drug release from osmotic pumps is independent of the release media's agitational intensity.

Table 1: Calibration curve of cefixime in methanol

Concentration	Absorbance
10	0.014
20	0.0292
30	0.0445
40	0.059
50	0.0719
60	0.0856

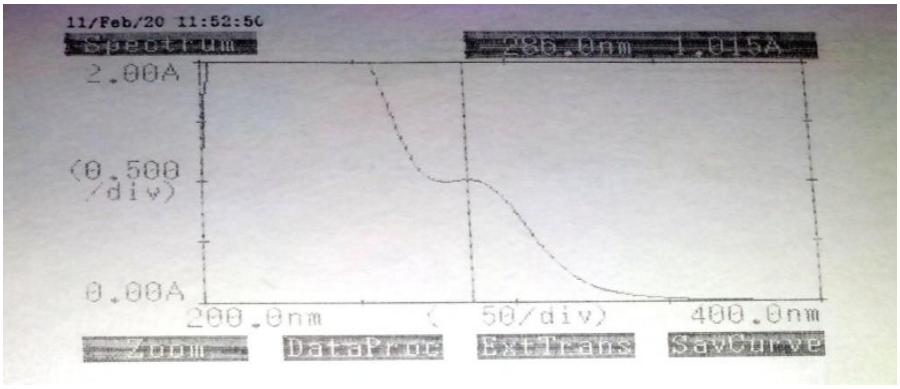

Fig. 1: Determination of cefixime wavelength

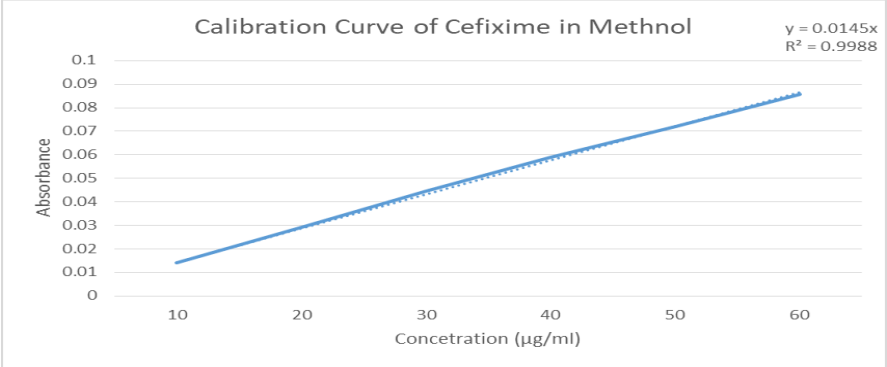

Fig. 2: Calibration curve of cefixime in methanol

Table 2: Calibration curve in phosphate buffer pH 6.8

Concentration	Absorbance
5	0.0124
10	0.0267
15	0.0394
20	0.0571
25	0.068
30	0.0847
35	0.0965
40	0.11
45	0.125
50	0.139

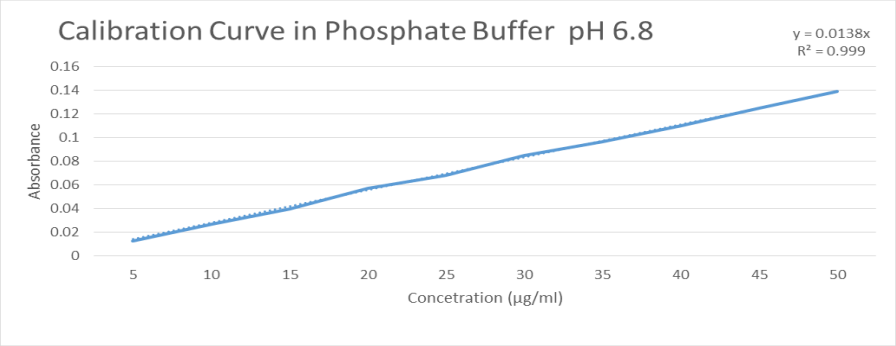

Fig. 3: Calibration curve in phosphate buffer pH 6.8

Table 3: Calibration curve in phosphate buffer pH 7.4

Concentration	Absorbance
5	0.0112
10	0.0255
15	0.0382
20	0.0559
25	0.0668
30	0.0835
35	0.0953
40	0.1088
45	0.1238
50	0.1378

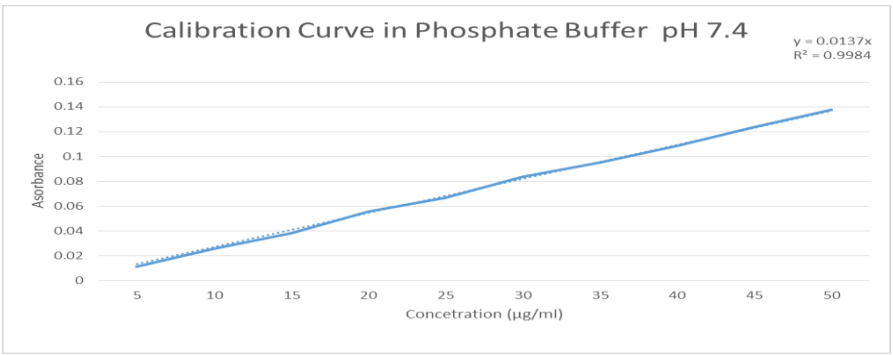

Fig. 4: Calibration curve in phosphate buffer pH 7.4

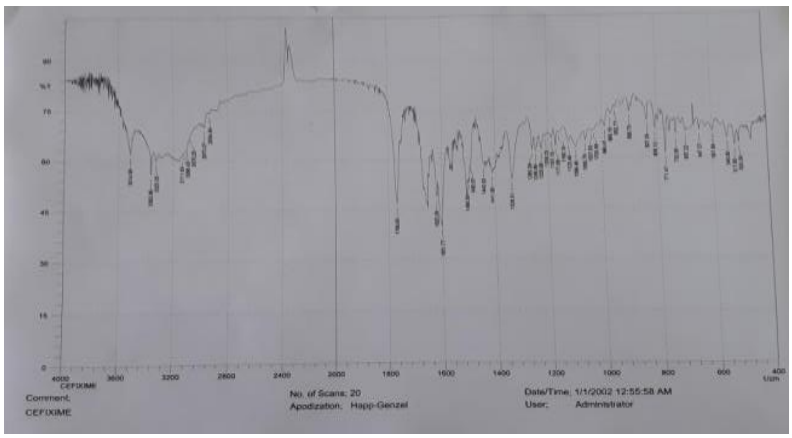

Fig. 5: Determination of IR spectroscopy of cefixime

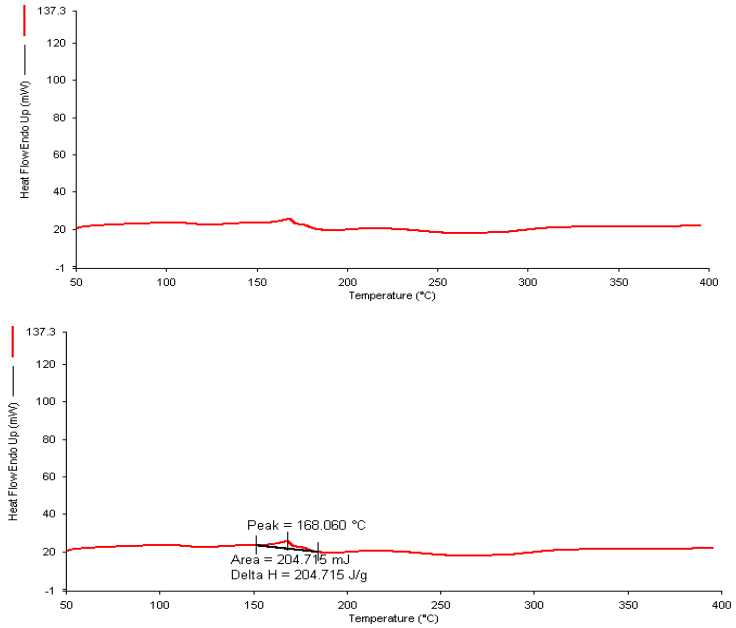

Fig 6: DSC Scanning

Table 4: Formulation Ingredients of Different Batch of Core Tablets

Name Of Ingredient	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	CP9
Drug (mg)	100	100	100	100	100	100	100	100	100
Sod. Chloride (mg)	60	60	60	80	80	80	100	100	100
MCC (mg)	105	105	105	85	85	85	65	65	65
SLS	13	13	13	13	13	13	13	13	13
Povidone K30	20	20	20	20	20	20	20	20	20
Mag. Stearate (mg)	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1

Table 5: Formulation Ingredients of Different Batch of Coated Tablets

Name Of Ingredient	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	CP9
Cellulose Acetate (%)	80	70	60	80	70	60	80	70	60
PEG 400 (%)	20	30	40	20	30	40	20	30	40

Table 6: Hardness of Coated Tablets Of different Batches

Hardness (Kg/Cm^2)									
No. Of Tablet	**CP1**	**CP2**	**CP3**	**CP4**	**CP5**	**CP6**	**CP7**	**CP8**	**CP9**
1	4.7	4.8	4.6	4.4	4.2	4.4	4.5	4.2	4.6
2	4.4	4.8	4.8	4.8	4.4	4.3	4.2	4.6	4.5
3	4.4	4.3	4.7	4.3	4.4	4.2	4.7	4.8	4.6
4	4.6	4.2	4.7	4.7	4.6	4.6	4.8	4.1	4.4
5	4.5	4.5	4.4	4.3	4.7	4.2	4.3	4.9	4.5
6	4.6	4.6	4.5	4.4	4.6	4.6	4.6	4.2	4.6
7	4.3	4.4	4.8	4.3	4.6	4.3	4.4	4.7	4.2
8	4.8	4.4	4.2	4.2	4.7	4.7	4.8	4.5	4.4
9	4.2	4.7	4.5	4.6	4.7	4.4	4.2	4.4	4.6
10	4.8	4.6	4.6	4.4	4.6	4.3	4.1	4.7	4.5

Table 7: Diameter (mm) Of Coated Tablets of Different Batches

Tablets Size (mm)									
No. Of Tablet	**CP1**	**CP2**	**CP3**	**CP4**	**CP5**	**CP6**	**CP7**	**CP8**	**CP9**
1	6.109	6.190	6.290	6.590	6.298	6.680	6.199	6.550	6.645
2	6.106	6.188	6.301	6.551	6.290	6.710	6.207	6.542	6.651
3	6.128	6.201	6.222	6.612	6.309	6.690	6.201	6539	6.639
4	6.145	6.170	6.287	6.509	6.310	6.702	6.196	6.561	6.609
5	6.119	6.210	6.350	6.640	6.340	6.700	6.210	6.560	6.650
6	6.111	6.183	6.299	6.602	6.330	6.599	6.211	6.599	6.649
7	6.125	6.192	6.309	6.617	6.329	6.669	6.208	6.499	6.626
8	6.087	6.063	6.310	6.619	6.317	6.701	6.204	6.535	6.641
9	6.117	6.177	6.287	6.630	6.326	6.608	6.194	6.553	6.599
10	6.115	6.209	6.302	6.639	6.264	6.647	6.209	6.520	6.638

Table 8: Friability of Coated Tablets of Different Batches

% Friability									
No. Of Tablet	**CP1 (%)**	**CP2 (%)**	**CP3 (%)**	**CP4 (%)**	**CP5 (%)**	**CP6 (%)**	**CP7 (%)**	**CP8 (%)**	**CP9 (%)**
1	0.0399	0.0372	0.0359	0.0653	0.0380	0.0639	0.0209	0.0380	0.0379
2	0.0487	0.0374	0.0349	0.0649	0.0379	0.0635	0.0219	0.0385	0.0374
3	0.0462	0.0369	0.0327	0.0651	0.0381	0.0642	0.0217	0.0379	0.0371
4	0.0481	0.0373	0.0356	0.0653	0.0380	0.0641	0.0218	0.0388	0.0369
5	0.0490	0.0375	0.0360	0.0654	0.0382	0.0640	0.0220	0.0390	0.0376
6	0.0395	0.0370	0.0358	0.0648	0.0369	0.0609	0.0221	0.0389	0.0375
7	0.0491	0.0376	0.0354	0.0650	0.0381	0.0638	0.0216	0.0375	0.0371
8	0.0438	0.0299	0.0361	0.0599	0.0375	0.0637	0.0214	0.0381	0.0372
9	0.0500	0.0368	0.0339	0.0652	0.0378	0.0629	0.0213	0.0391	0.0370
10	0.0482	0.0365	0.0345	0.0647	0.0359	0.0638	0.0215	0.0369	0.0359

Table 9: Weight Gain After coating of Different Batches

Weight Gain (mg)									
No. Of Tablet	**CP1 (mg)**	**CP2 (mg)**	**CP3 (mg)**	**CP4 (mg)**	**CP5 (mg)**	**CP6 (mg)**	**CP7 (mg)**	**CP8 (mg)**	**CP9 (mg)**
1	309	308	311	310	309	308	310	310	309
2	311	310	309	312	311	310	309	312	311
3	310	309	310	311	310	309	308	311	309
4	309	308	309	310	311	310	310	310	310
5	310	309	310	311	310	309	309	311	310
6	311	310	311	310	309	310	308	311	309
7	311	309	310	312	311	309	309	312	311
8	310	308	309	310	309	308	309	310	311
9	310	310	311	311	310	310	310	311	309
10	311	310	310	312	311	310	308	312	310

Table 10: Drug Content (%) in different batches

% Drug Content									
No. Of Tablet	**CP1 (%)**	**CP2 (%)**	**CP3 (%)**	**CP4 (%)**	**CP5 (%)**	**CP6 (%)**	**CP7 (%)**	**CP8 (%)**	**CP9 (%)**
1	96.59	97.89	98.90	98.91	98.90	99.19	99.43	99.54	99.71
2	95.62	97.91	98.89	98.94	98.88	99.24	99.41	99.50	99.75
3	96.63	96.95	97.99	98.95	98.85	99.23	99.42	99.53	99.69
4	96.58	97.94	98.92	98.96	97.98	99.18	98.99	99.51	99.70
5	94.64	97.96	98.91	98.96	98.89	99.25	99.45	99.55	99.77
6	93.61	96.97	98.87	97.99	98.87	99.26	99.40	99.58	99.65
7	96.65	97.92	98.88	98.97	98.86	99.22	99.46	99.56	99.74
8	96.60	97.93	98.85	98.93	98.79	98.99	99.44	99.52	99.72
9	96.57	96.99	97.98	98.92	98.82	99.20	98.98	99.49	99.76
10	96.55	97.90	98.86	98.83	98.83	99.21	99.39	99.48	99.73

Table 11: Mean Value of All Parameters for Coated Tablets

Formulation Code	**Diameter (mm)**	**Average Weight (mg)**	**Hardness (Kg/Cm^2)**	**Friability (%)**	**Content Uniformity (%)**
CP1	6.11 ± 1.24	310 ± 1.03	4.5 ±0.14	0.0490	96.64 ± 0.45
CP2	6.12 ± 1.23	309 ± 1.03	4.5 ± 0.16	0.0375	97.96 ± 0.87
CP3	6.35 ± 0.98	310 ± 0.96	4.8 ± 0.15	0.0360	98.89 ± 0.24
CP4	6.64 ± 1.3	311 ± 1.49	4.3 ± 0.12	0.0654	98.91 ± 0.54
CP5	6.34 ± 0.2	310 ± 1.37	4.4 ± 0.18	0.0382	98.90 ± 0.59
CP6	6.70 ± 1.6	309 ± 1.15	4.2 ± 0.11	0.0640	99.25 ± 0.84
CP7	6.21 ± 0.01	309 ± 1.08	4.3 ± 0.15	0.0220	99.45 ± 0.67
CP8	6.56 ± 0.11	311 ± 1.24	4.6 ± 0.23	0.0390	99.55 ± 0.66
CP9	6.65 ± 1.23	310 ± 1.74	4.5 ± 0.89	0.0376	99.77 0.75

(n=10) Mean ± SD

Table 12: Dissolution Profile

S.No.	**Parameter**	**Specification**
1	Dissolution medium	Buffer (pH 7.4)
2	Temperature	37±0.5˚C
3	Volume of media	900 ml
4	Rotation speed	50 rpm
5	Volume withdrawn	5 ml
6	Running time	24 hrs. in pH 7.4

Table 13: In Vitro Drug Release Data of Different Batches of CPOP Tablets

	% drug release								
Time (hrs.)	**CP1**	**CP2**	**CP3**	**CP4**	**CP5**	**CP6**	**CP7**	**CP8**	**CP9**
0	0	0	0	0	0	0	0	0	0
0.5	0.432787	0.704508	0.76721	0.77582	0.8545	0.8508	0.987	0.9823	0.9986
1	0.506503	1.061291	1.17229	1.18463	1.0621	1.2834	1.7633	1.86409	1.9949
1.5	1.882483	2.36655	2.42862	2.47786	2.3665	2.749	3.7378	3.6011	3.8464
2	3.071585	3.72623	4.27985	4.4393	4.6975	4.9578	5.9877	5.1224	6.2214
3	5.210107	6.675145	7.56052	7.75965	7.7414	8.4514	9.7261	10.1407	12.074
4	7.684965	9.001462	10.2142	10.2346	10.3019	11.1026	15.0023	14.9811	16.2612
5	9.880018	14.12407	15.2788	15.5572	15.3062	16.705	19.8273	20.6844	23.6878
6	12.93994	18.36551	19.9188	20.0788	19.3678	21.8755	24.3514	26.5133	30.7865
7	14.4509	21.40684	22.4453	23.5997	26.3225	26.7246	29.0375	32.163	36.0874
8	17.47713	24.14213	24.9978	27.7426	30.5114	31.3693	34.2028	38.4371	43.163
9	19.88433	27.14588	30.4004	31.65	35.916	37.067	39.0122	43.8541	49.8721
10	21.98925	31.9426	34.9023	35.8548	40.1291	42.7848	44.4173	49.5596	56.7206
11	23.7937	35.5558	39.0184	41.2565	44.9332	48.4937	49.8256	55.5672	62.7642
12	25.59649	40.05757	44.8143	45.4697	48.5454	52.4097	55.235	60.9789	71.7689
24	31.23374	42.1741	60.97806	63.14227	71.5733	81.7141	86.3396	92.6831	96.2476

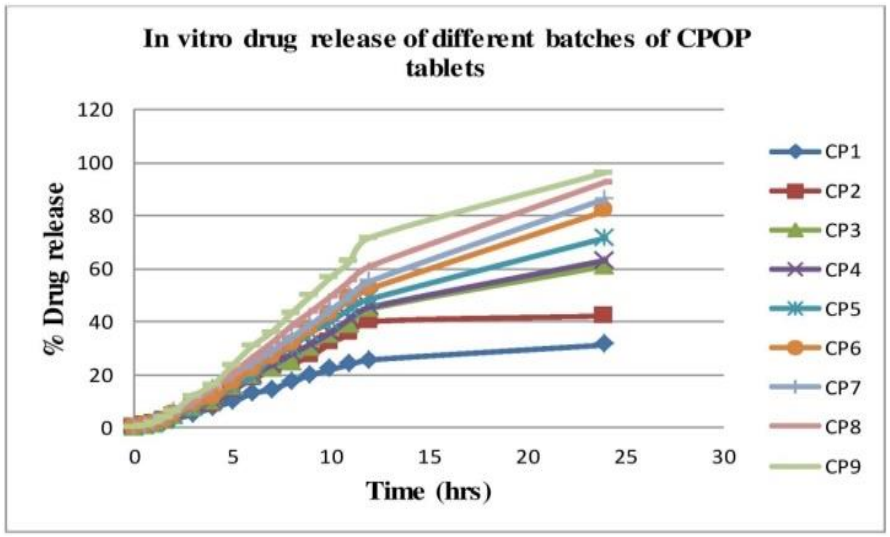

Fig. 7: In Vitro Drug Release of Different Batches of CPOP Tablets

Table 14: In Vitro Release as A Function of % Weight Gain

Time (hrs.)	3% wt. gain (approx.) after 1st coating	6% wt. gain (approx.) after 2nd coating	8% wt. gain (approx.) after 3rd coating
0	0	0	0
0.5	0.9986	0.7069	0.5877
1	1.9949	1.6391	1.5278
1.5	3.8464	3.5008	2.7010
2	6.2214	5.1587	4.7362
3	12.074	9.3108	7.9895
4	16.2612	12.1139	10.5510
5	23.6878	18.7032	15.7346
6	30.7865	23.0425	19.7971
7	36.0874	27.9070	24.4809
8	43.163	33.3722	28.1522
9	49.8721	36.9880	32.6546
10	56.7206	40.2948	37.4607
11	62.7642	46.2892	42.2678
12	71.7689	52.2068	47.2824

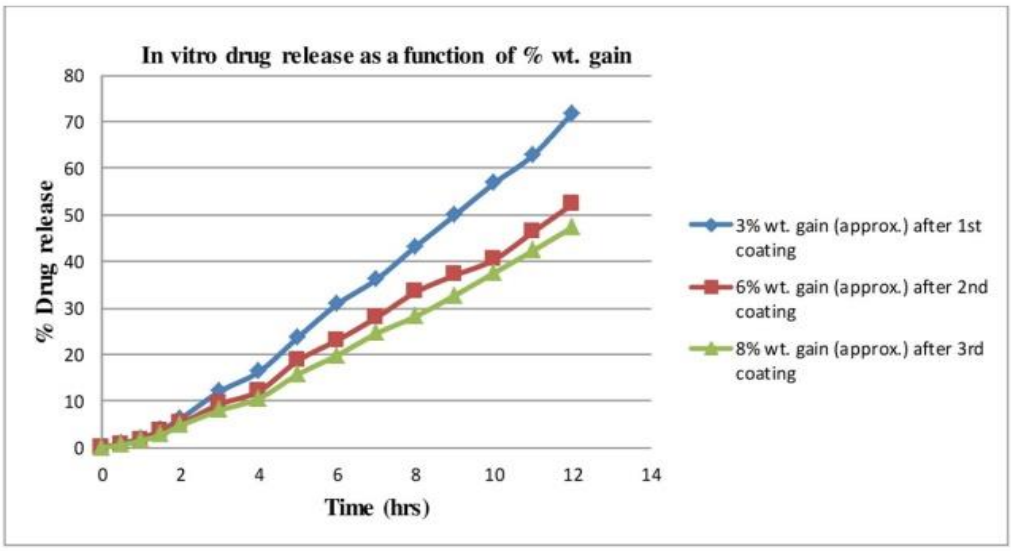

Fig. 8: In Vitro Drug Release as A function of % Wt. Gain

Table 15: In Vitro Drug Release as A Function of External Osmotic Pressure

Time (hrs)	2% NaCl	5% NaCl
0	0	0
0.5	0.895082	0.69959
1	1.689399	1.201428
1.5	4.115915	3.105014
2	5.936749	5.832787
3	10.98952	9.24159
4	15.58615	13.65035
5	20.60176	17.76854
6	24.2749	22.90085
7	30.331	26.75394
8	34.15936	31.6457
9	40.75415	36.45364
10	45.27274	40.36466
11	48.58449	45.46592
12	54.28004	48.48219

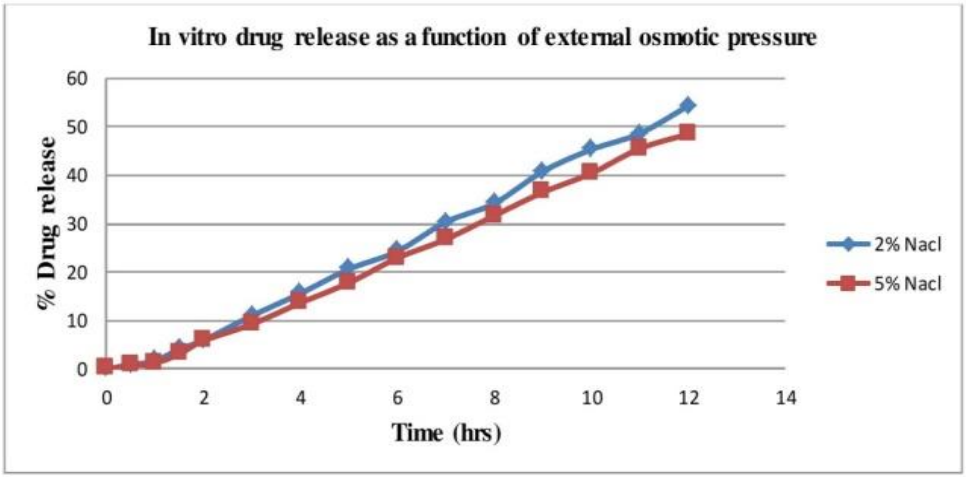

Fig. 9: In Vitro Drug Release as A function of External Osmotic Pressure

Table 16: In Vitro Drug Release as A function of Pore Former Concentration

Time (hrs.)	40% Pore former	50% Pore former
0	0	0
0.5	0.9986	1.6391
1	1.9949	3.5894
1.5	3.8464	6.7851
2	6.2214	11.7634
3	12.074	16.7698
4	16.2612	23.4637
5	23.6878	30.7032
6	30.7865	39.0425
7	36.0874	45.9070
8	43.163	51.3722
9	49.8721	62.9880
10	56.7206	70.2948
11	62.7642	81.2892
12	71.7689	92.2068

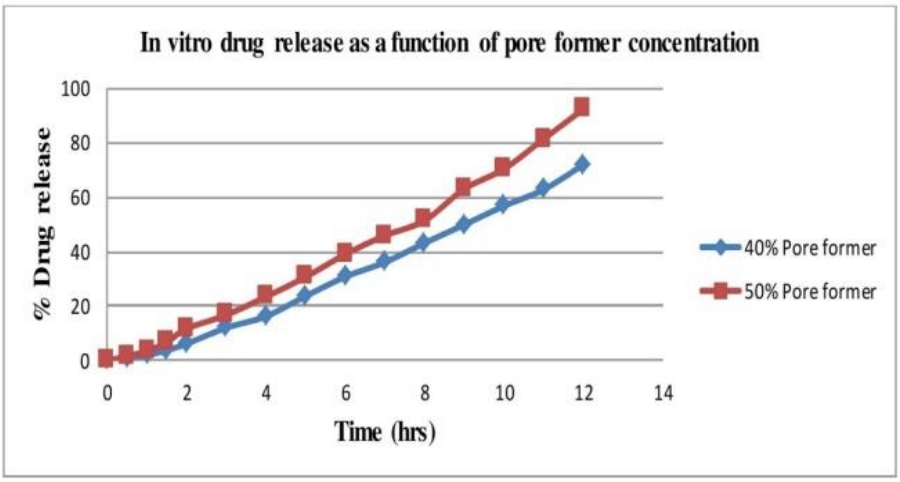

Fig. 10: In Vitro Drug Release as A Function of Pore Former Concentration

Table 17: In Vitro Drug Release as A function of Agitation Intensity

Time	50 RPM	100 RPM
0	0	0
0.5	0.9986	0.9997
1	1.9949	1.9749
1.5	3.8464	3.6066
2	6.2214	7.1388
3	12.074	14.1403
4	16.2612	18.8911
5	23.6878	22.6845
6	30.7865	34.5133
7	36.0874	38.7895
8	43.163	47.7894
9	49.8721	50.8543
10	56.7206	57.5764
11	62.7642	65.3487
12	71.7689	72.4585

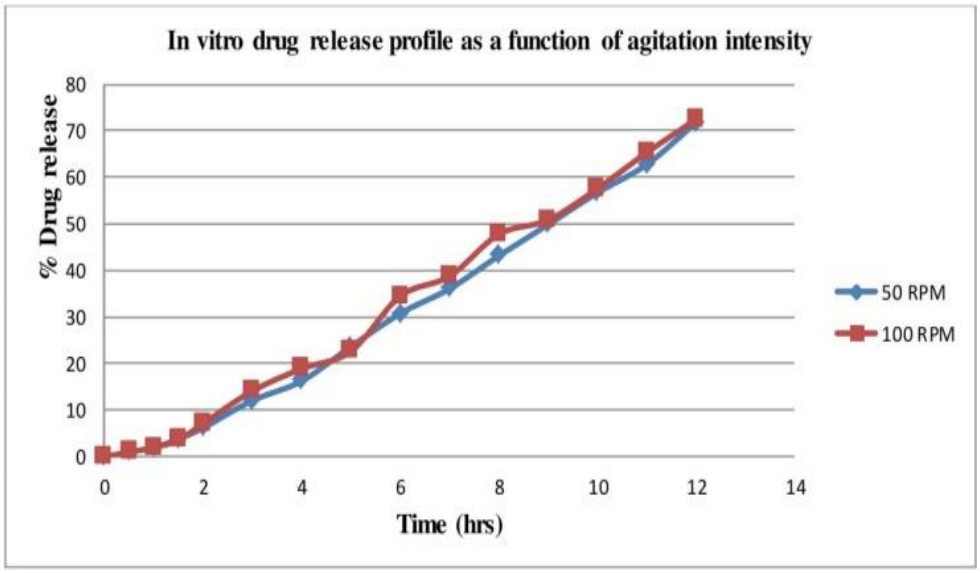

Fig. 11: In Vitro Drug Release Profile as A function of Agitation Intensity

Table 18: % Cumulative Drug Release of CP9 Batch for Zero Order Model

Time (hrs.)	% Cumulative Drug Release
0	0
0.5	0.982377
1	1.984966
1.5	3.606619
2	5.138859
3	10.19365
4	14.97236
5	20.79341
6	26.67638
7	32.41227
8	39.10566
9	44.37127
10	50.2627
11	56.48448
12	62.14185

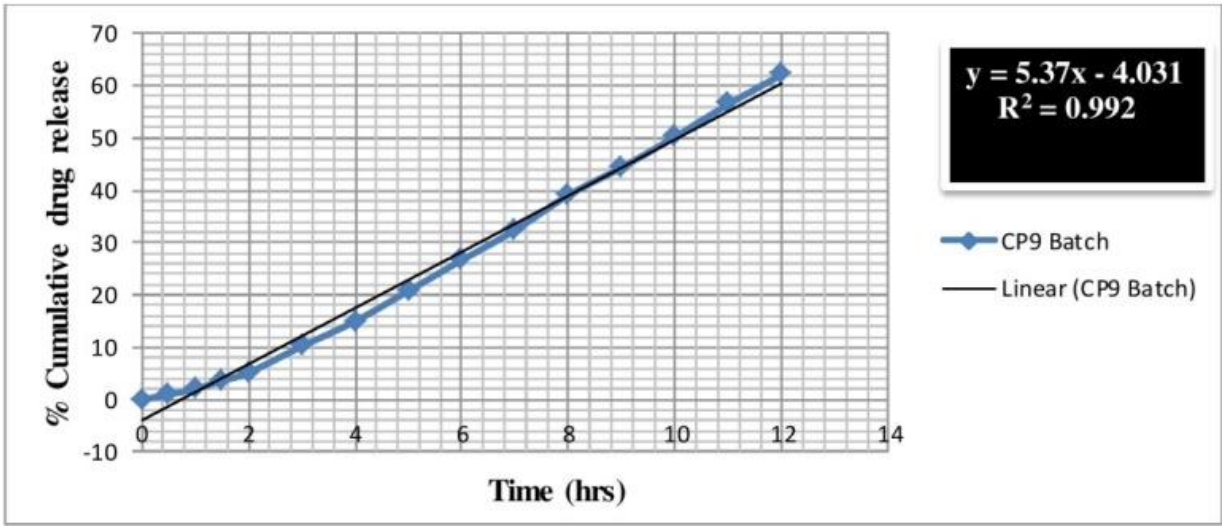

Fig. 12: % Cumulative Drug Release of CP9 Batch for Zero Order Model

Table 19: Log % Cumulative Drug Remaining For First Order Model

Time (hrs.)	Log % Cumulative Drug Remaining
0	2
0.5	1.995712
1	1.991293
1.5	1.984047
2	1.977088
3	1.953307
4	1.92956
5	1.898761
6	1.8655244
7	1.829868
8	1.784577
9	1.745299
10	1.696682
11	1.638644
12	1.578159

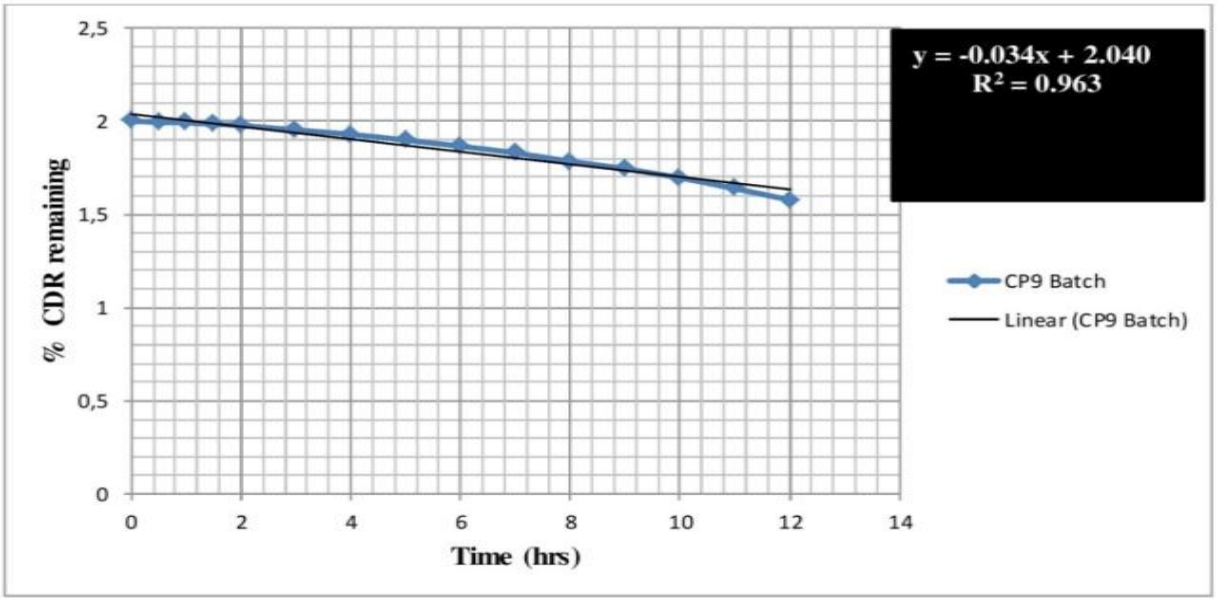

Fig. 13: % Cumulative Drug Release for First Order Model

Table 20: 2.30 r^2 Values of CP9 Batch in Different Kinetic Models

Batch	Zero Order		First Order	
CP9	r^2	K_0	r^2	K_1
	0.9927	-4.031	0.9635	2.04

CONCLUSION

In the present study, a controlled release formulation of cefixime based on osmotic technology was developed. The release from the developed formulation was independent of pH and agitational intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. Drug release data from cefixime formulation fitted well into zero-order kinetics, indicating the release of drug load independent. Drug release was directly proportional to the initial pore level but inversely related to the membrane weight. The release was inversely associated with the release media's osmotic pressure, confirming osmotic pumping as the central mechanism of release.

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