The Pharma Innovation Journal 2018; 7(10): 201-211

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(10): 201-211

www.thepharmajournal.com
Received: 27-08-2018
Accepted: 28-09-2018

G Srikanth
Assistant Professor, Department of Pharmaceutics, Vision College Of Pharmaceutical Sciences and Research, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India

Munija Pancheddula
Research Scholar, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India

Correspondence
Munija Pancheddula
Research Scholar, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India

Design and Evaluation of Once a Day Matrix Tablet of Cephalexin

G Srikanth and Munija Pancheddula

Abstract
In the present research, an attempt has been made to formulate extended release matrix tablets of a cephalosporin antibiotic cephalexin. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, easy in manufacturing, high level of reproducibility and easy of scale up and process validation. Cephalexin mono hydrate, β-lactam antibiotic is a broad-spectrum antibiotic for treatment of wide range of bacterial infections, including urinary tract infections and respiratory tract infections 5-7, hence, was chosen as a model drug with an aim to develop a extended release matrix tablet. Different formulations were prepared by wet granulation method by using different polymers like HPMC, Microcrystalline cellulose and carbomer with different ratios were used in the development of formulations. The prepared tablets were evaluated for precompression and post compression parameters with different ratios. All the formulations showed compliance with pharmacopoeial standards. The effect of polymer loading in *in-vitro* drug release and the mechanism of release/dissolved was studied by different mathematical models. Dissolution profile of different formulation shows that the rate of drug release for Cefdinir from a hydrophilic matrix tablets is controlled by the polymer composition of matrix, higher the polymer concentration slower the drug release. By judiciously varying the ratio of drug to polymer, the desire matrix characteristics can be obtained to control initial burst and modulate drug releasehe selected formulations were subjected to stability studies as per ICH guidelines at different temperature and humidity conditions. **:** It can be concluded that among all the formulations the combination of Methocel K4M (5%) and Methocel E 50 LV (15%) as a rate retarding polymers was considered as the optimized formulation in the present research work.

Keywords: Cephalexin, HPMC, Microcrystalline cellulose and carbomer

1. Introduction
Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if an extended therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide extended drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms [1] Sustained release (SR) tablet formulations are much enviable and chosen for such therapy because they offer better patient compliance, maintain uniform drug levels in the systemic circulation, reduce dose and side effects. To obtain a better drug release profile in oral controlled drug delivery a variety of polymer matrix systems have been used [2].
Cefdinir is a semi-synthetic third generation broad-spectrum oral cephalosporin antibiotic and is active against Grampositive and Gram-negative rods. It is used in the treatment of acute chronic bronchitis, rhinosinusitis and Pharyngitis [3]

Matrix tablets
These are the simplest & least expensive systems for controlled drug delivery. Their processing is reproducible & is similar to that conventional system. The polymer or other carrier is homogeneously mixed with drug.
Drug release from the bulk of matrix involves two matrix mechanisms:

1. The Erosion rate of the matrix determines the drug release state in matrices governed by erosion or dissolution

$$\left(\frac{dm}{dt}\right) = S\left(\frac{dx}{dt}\right) f(c) \qquad Eq\ (1)$$

Where:
$\left(\frac{dm}{dt}\right)$- Drug release rate
S - Surface area
$\left(\frac{dx}{dt}\right)$- Matrix erosion rate
$f(c)$- Drug Concentration gradient

2. The diffusion through a barrier membrane describes drug release in insoluble coating via fick's second law of diffusion.

$$\left(\frac{dm}{dt}\right) = DSK\ \frac{(Cd-Cr)}{h} \qquad Eq\ (2)$$

Where:
D – Diffusion coefficient
S – Exposed surface area
K –Partition coefficient
$(Cd - Cr)$– Drug concentration gradient

Advantages of matrix systems
Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipments. Secondly, development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

Limitations of the matrix systems
As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome.
When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

Types of matrix systems
The matrix system can be divided into two categories depending on the types of retarding agent or polymeric materials.

Hydrophobic matrix system
This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release.

Hydrophilic matrix system
The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate.

Materials and Methods
Materials Used: Cephalexin was obtained as a gift sample from Aurobindo laboratories, Hyderabad, India. Micro crystalline cellulose, Lactose monohydrate, Hydroxy propyl methyl cellulose, Carbomer, Sodium Lauryl Sulphate, Polyoxyl 40 stearate, Colloidal silicon dioxide, Magnesium stearate were obtained from SD fine Chem. Ltd. Mumbai, India.

Methodology
Required quantities of Cephalexin, lactose monohydrate (Lactochem), polymers were weighed separately as per formula. Weighed materials were co sifted #20 mesh.

Preparation of binder solution
To the 150 ml of purified water, total weighed quantities of sodium lauryl sulphate and Myrj S 52 were slowly added during stirring at 500 rpm until clear solution formed (less impeller speed is desirable to prevent foam while stirring with surfactants). Additional quantity of purified water was used as binder to get desired granulation end point.
Co-sifted blend was loaded into rapid mixer granulator (RMG) bowl. Granulation was carried out, above formed granulated wet mass was shifted into Rapid Dryer bowl and then dried. The granules obtained were sized through #20 mesh. Calculated quantities extra granular material was weighed and passed through #20 mesh along with granules. Required quantities of Aerosil 200(Anhydrous colloidal silicon dioxide) and magnesium stearate were weighed, passed through #60 mesh and blended with above granules mixture for 3 min. Finally blend was compressed with 22 × 10 mm capsule shape D- type tooling punch using 8 station compression machine.

Table 1: The Composition of Matrix tablets of cephalexin

Ingredients	F1	F2	F3	F4	F5	F6
Cephalexin	500.00	500.00	500.00	500.00	500.00	500.00
Lactose monohydrate	100.00	100.00	108.00	233.00	233.00	233.00
Avicel PH 101	225.00	225.00	215.00	120.00	120.00	162.00
Sodium lauryl sulphate	8.00	8.00	10.00	24.00	24.00	24.00
Myrj S 52	2.00	2.00	2.00	5.00	5.00	5.00
Carbopol 974 NF	100.00	100.00	-	-	-	-
Methocel K4M CR	-	-	360.00	180.00	180.00	96.00
Methocel E 50 LV	-	-	-	60.00	60.00	95.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methocel E50 LV	-	-	-	-	-	0.50
Carbopol 971NF	50.00	-	-	-	-	-
Avicel PH 102	-	50.00	-	60.00	-	60.00
Aerosil 200	10.00	10.00	6.00	12.00	12.00	12.00
Magnesium stearate	5.00	5.00	6.00	12.00	12.00	12.00
Total wt (mg)	1000.00	1000.00	1200.00	1200.00	1140.00	1200.00

Table 2: The Composition of Matrix tablets of cephalexin

Ingredients	F7	F8	F9	F10	F11	F12	F13
Cephalexin	500.00	500.00	500.00	500.00	500.00	500.00	500.00
Lactose monohydrate	233.00	233.00	233.00	233.00	233.00	239.00	221.00
Avicel PH 101	162.00	114.00	114.00	114.00	114.00	114.00	114.00
Sodium lauryl sulphate	24.00	24.00	24.00	24.00	24.00	24.00	24.00
Myrj S 52	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Carbopol 974 NF	-	-	-	-	-	-	-
Methocel K4M CR	96.00	60.00	60.00	60.00	60.00	60.00	60.00
Methocel E 50 LV	95.50	179.50	179.50	179.00	178.00	179.50	179.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methocel E50 LV	0.50	0.50	0.50	1.0	-	0.50	0.50
Carbopol 971NF	-	-	-	-	-	-	-
Avicel PH 102	-	60.00	-	60.00	60.00	60.00	60.00
Aerosil 200	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Magnesium stearate	12.00	12.00	12.00	12.00	12.00	6.00	24.00
Total wt (mg)	1140.00	1200.00	1140.00	1200.00	1200.00	1200.00	1200.00

Evaluation Parameters and Procedure

1. Preformulation parameters

A. Determination of flow properties

20 gms of Drug was taken in 100 ml measuring cylinder which was placed in Electro lab Tapped Density Apparatus (method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped 500 times and volume was measured. Then further an additional 750 tapings were repeated (If the difference between the two volumes is less than 2%, this volume considered as the final tapped volume). No difference was noted between the volumes between two tapings (500 and 750). If the difference between the two volumes is less than 2%, this volume is considered as final tapped volume.

B. Determination of solubility

Solubilities were determined by adding an amount of compound well in excess of its saturation solubility to the solvent. Excess drug substance was shaken in each buffer at ambient temperature for several hours. The samples are then centrifuged and solubility is determined by analyzing an aliquot of the supernatant after 24hrs.

C. Moisture content determination [14, 15]

Moisture content was determined by

- Infrared drying (gravimetric method)
- Karl Fischer titrations (chemical method)

D. Particle Size Analysis

Several different sieve and powder agitation devices are commercially available, all of which may be used to perform sieve analyses. However, the different methods of agitation may give different results for sieve analyses and endpoint determinations because of the different types and magnitude of the forces acting on the individual particles under test. Methods using mechanical agitation or electromagnetic agitation, and that can induce either a vertical oscillation or a horizontal circular motion, or tapping or a combination of both tapping and horizontal circular motion is available. Entrainment of the particles in an air stream may also be used.

$$\text{For material retained} = \frac{\text{Weight of retained material}}{\text{Total weight of sample}} \times 100$$

$$\text{For material pass} = \frac{\text{Total weight of sample - Weight of retained material}}{\text{Total weight of sample}} \times 100$$

2. Drug – Excipients compatibility studies

Drug- excipient compatibility study by using Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) Study was carried out to know the interaction among drug and the excipients. Pure drug and optimized formulation were subjected to the study. 5-15mg of sample to be analysed was taken in the pierced DSC aluminium pan and Scanned in the temperature range of 50-400 ^{0}C. The heating rate was 20 ^{0}C/min; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyser (perkin elemer-4000) was used for this purpose.

3. Post compression Evaluation

Physicochemical characterization of tablets: The prepared cefidinir matrix tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

A. Weight variation: The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by ± 10% and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity.

The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) X 100

The average weight of tablets in each formulation was calculated and presented with standard deviation

Table 3: Pharmacopoeial specifications for tablet weight variation

Average weight of tablets (mg)	Maximum% of difference allowed
80 or less	± 10
More than 80 but less than 250	± 7.5
250 or more	± 5

B. Tablet Thickness

The Thickness and diameter of the tablets from production run is carefully controlled. Thickness can vary with no change in weight due to difference in the density of granulation and the pressure applied to the tablets, as well as the speed of the tablet compression machine. Hence this parameter is essential for consumer acceptance, tablet uniformity and packaging. The thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablet is calculated and presented with standard deviation.

C. Tablet Hardness

Tablet hardness is defined as the force required to breaking a tablet in a diametric compression test.Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm2 .

D. Friability

Tablet hardness is not an absolute indicator of the strength because some formulations when compressed into very hard tablets lose their crown positions. Therefore another measure of the tablet strength, its friability, is often measured. Tablet strength is measured by using Roche friabilator. Test subjects to number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as Friability (%) = Initial weight of 10 tablets – final weight of 10 tablets / Initial weight of 10 tablets X 100

F (%) = [Wo-W/WO] X100

Where, Wo is the initial weight of the tablets before the test and W is the final weight of the tablets after test.

E. Assay

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100 ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 290 nm using pH 6.8 phosphate buffer.

F. *In-vitro* dissolution studies

The *in-vitro* dissolution studies were performed using USP type II dissolution apparatus at 50 rpm. Dissolution test was carried out for a total period of 24hrs using 0.1 N HCl (pH 1.2) solution (900ml) as dissolution medium at 37±0.5 ºC for first 2 hrs and 6.8 pH phosphate buffer solution (900ml) for the rest of the period. An aliquot (5ml) sample was withdrawn at specific time intervals and replaced with fresh medium to maintain a constant volume. The samples were filtered, and analyzed by UV spectrophotometer at 290nm. The concentration was calculated using standard calibration curve.

Kinetic analysis of dissolution data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative% drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative% drug released versus log time.

1. Zero order kinetics:

Zero order release would be predicted by the following equation:-

At = A0 – K0t

Where, At = Drug release at time't'.

A0 = Initial drug concentration

K0 = Zero – order rate constant (hr-1).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero –

order release kinetics, with a slope equal to K0.

2. First order kinetics

First – order release would be predicted by the following equation:-

Log C = log C0 – Kt /2.303

Where, C = Amount of drug remained at time 't'.
C0 = Initial amount of drug.
K = First – order rate constant (hr-1).
When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

3. Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.
$Q = [D\square / \square (2\ A - \square\ Cs)\ Cst]^{1/2}$
Where, Q = Amount of drug released at time't'.
D = Diffusion coefficient of the drug in the matrix.
A = Total amount of drug in unit volume of matrix.
Cs = the solubility of the drug in the matrix.
□□ = Porosity of the matrix.
□□ = Tortuosity.
t = Time (hrs) at which 'q' amount of drug is released.
Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant.
Then equation becomes: Q = Kt1/2
When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

4. Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the mucoadhesive tablets of mosapride citrate, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

Mt / Ma = Ktn

Where, Mt / Ma = the fraction of drug released at time't'.
K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.
n = Diffusion exponent related to the mechanism of the release.
Above equation can be simplified by applying log on both sides,

Log Mt / Ma = LogK + n Logt

1. When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and1

Results and Discussion

1. Flow properties

Table 4: Flow properties of API

S.No.	Wt (g)	V_0 (ml)	V (ml)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index	Hausner'sRatio
1	22.44	40.0	26.0	0.561	0.863	35.00	1.54
2	21.96	40.0	25.0	0.549	0.878	37.50	1.60
3	22.15	40.0	27.0	0.554	0.820	32.50	1.48
Avg.	22.18	40.00	26.00	0.555	0.854	35.00	1.54

Preformulation studies of drug were performed to characterize the API. The powder flow properties of API were studied to evaluate compressibility of the drug, since it has to be formulated as tablet. The results obtained are bulk density 0.555 mg/ml and tapped density was 0.854 mg/ml and Hausner's ratio 1.54. The results showed that the compressibility of the API was 35 which indicate that the drug has poor flow properties. If compressibility of drug was good then direct compression method can be employed to formulate tablets, since flow property was poor necessary measures should be taken to increase the values of compressibility and Hausner's ratio of drug powder.

2. Solubility studies

The solubility of Cephalexin was studied in different media.The results of the study are compiled below in table no.5.

Table 5: Solubility study data of Cephalexin monohydrate

Medium	Solubility (mg/ml)
Water	27.6
6.8 pH phosphate buffer	36.5
0.1N Hcl buffer	74.8

From all the above pH solubility profile results, it has been observed that the solubility of drug is 36.5mg/ml in pH 6.8 Phosphate Buffer and 74.8mg/ml in 0.1 N Hcl

3. Moisture content determination

Moisture content was determined
By moisture analyzer (Sartorius) and the result was 1.21% w/w at 105 ^{0}C in AUTO mode.
By Karl Fischer titration method - 1.34% w/w of moisture content was determined.

4. Particle size analysis

Table 6: Particle size analysis of Cefdinir API

S. No	Mesh No	Pore size*	W_o	W1	W1- W_o	% Retained
1	#30	600 µm	383.7	383.9	0.2	0.8
2	#40	425 µm	367	367.5	0.5	2
3	#60	250 µm	332.1	336.4	4.3	17.2
4	#80	180 µm	347.9	365.1	17.2	68.8
5	#100	150 µm	338.4	340	1.6	6.4
8	#200	75 µm	325.2	325.5	0.3	1.2
9	#200 P	50 µm	497.3	498.6	1.3	5.2

* According to USP32

By the above results it was observed that the 68.8% of particles are retained on the #80 mesh which have 180 µm aperture size and 82.8% of particles are passed through the #60 mesh which have 250 µm aperture size. Therefore it was concluded that major amount of particles have its size range of 180 µm to 250 µm.

5. Drug – Excipient compatibility studies

Drug - excipient compatibility study by Differential Scanning Calorimetry

DSC thermogram of pure drug and optimized formulaton are shown in figure 1&2. There were two significant events appeared in the DSC study of cephalexin monohydrate. Drug was shown sharp endothermic peak at 167.87 ºC and exothermic peak shown at 203ºC and optimized formulation containing different grades of Methocel was shown 76.45 ºC. From the DSC study, it can be concluded that there was no interaction between pure drug and polymers used in the study.

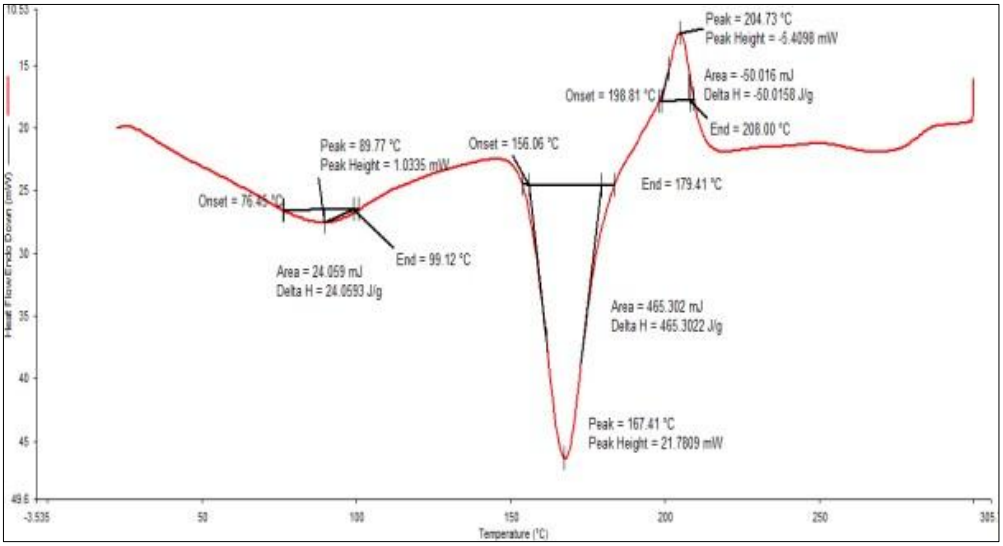

Fig 1: DSC Thermogram of pure drug

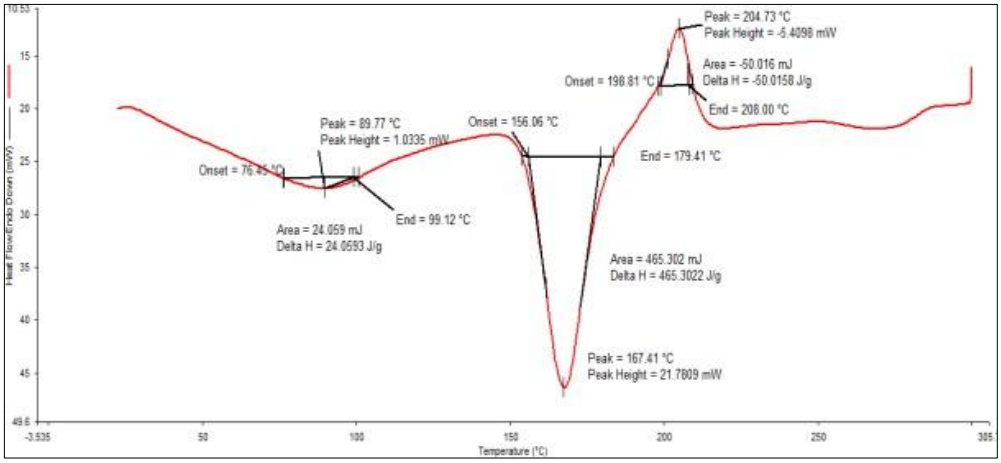

Fig 2: DSC Thermogram of optimized formulation

6. Potency calculation

Actual amount of the API per tablet to be taken is

$$= \frac{\text{specified amount of API in formula}}{\text{Assay(On as is basis)}} \times 100 = \frac{500}{97.7} \times 100 = 511.77 \text{ mg}$$

Calculated amount was compensated with the filler (lactose monohydrate or Avicel PH 101)

7. Physical evaluation of final blend

Table 7: Physical evaluation of tablets (F1-F9)

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density(g/cc)	0.527	0.595	0.498	0.524	0.511	0.531	0.515	0.54	0.521
Tapped density(g/cc)	0.60	0.681	0.654	0.663	0.645	0.697	0.688	0.716	0.691
Compressibility index (%)	12.16	12.62	23.85	20.96	20.77	23.81	25.14	24.58	24.60
Hausner's ratio	1.13	1.14	1.31	1.26	1.26	1.31	1.33	1.32	1.32
Colour	Light yellow	Light yellow	Light yellow	Light yellow	Light yellow	Light yellow	Light yellow	Light yellow	Light yellow
Surface	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Thickness(mm)	5.61 mm	5.54 mm	5.91 mm	5.64 mm	5.16 mm	5.55 mm	5.12 mm	5.45 mm	5.21 mm
Hardness(kp)	19.0-20.0	19.0-20.0	12.0-12.5	10.5-11.0	9.0-9.5	9.5-10.1	8.0-8.5	10.5-12.0	10.0-10.5
Weight(mg)	1000 ± 0.44	1000 ± 0.49	1200 ± 0.07	1200 ± 0.66	1140 ± 0.49	1200 ± 0.55	1140 ± 0.64	1200 ± 0.11	1140 ± 0.86
Friability (%)	0.12 ± 0.05	0.16 ± 0.05	0.57 ± 0.05	0.69 ± 0.05	0.61 ± 0.05	0.44 ± 0.07	0.66 ± 0.05	0.41 ± 0.04	0.33 ± 0.03
Assay	99.59%	99.12%	100%	99.45%	99.08%	99.15%	98.99%	98.12%	98.89%

Table 8: Physical evaluation of tablets (F10-F13)

	F10	F11	F12	F13
Bulk density(g/cc)	0.525	0.524	0.528	0.501
Tapped density(g/cc)	0.651	0.663	0.657	0.622
Compressibility index (%)	19.35	20.96	19.63	19.45
Hausner's ratio	1.24	1.26	1.24	1.24
Colour	Light yellow	Light yellow	Light yellow	Light yellow
Surface	Smooth	Smooth	Slight smooth	Smooth and very shine
Thickness(mm)	5.37 mm	5.64 mm	5.37 mm	5.64 mm
Hardness(kp)	12.5-13.5	10.5-11.0	10.5-12.5	9.5-11.0
Weight(mg)	1200 ± 0.11	1200 ± 0.66	1200 ± 0.14	1200 ± 0.66
Friability (%)	0.35 ± 0.04	0.69 ± 0.05	0.55 ± 0.04	0.69 ± 0.05
Assay	99.54%	98.47%	99.21%	98.47%

8. Dissolution profiles

Table 9:% cumulative drug release

Time (hr)	Cumulative% drug release			
	F1	F3	F4	F5
1	10 ± 5.99	9±4.9	15±5.5	11±6.0
2	32 ± 5.44	17±3.5	16±2.6	21±5.0
4	71 ± 3.57	23±2.5	25±3.3	35±4.1
8	91 ± 3.21	33±2.9	40±3.5	62±4.0
12	98 ± 4.53	40±2.1	50±4.6	77±3.7
16	99 ± 3.55	47±1.5	59±1.6	84±4.0
20	100 ± 2.63	53±1.0	66±1.1	90±2.8
24	100 ± 0.00	58±0.9	74±0.8	94±1.5

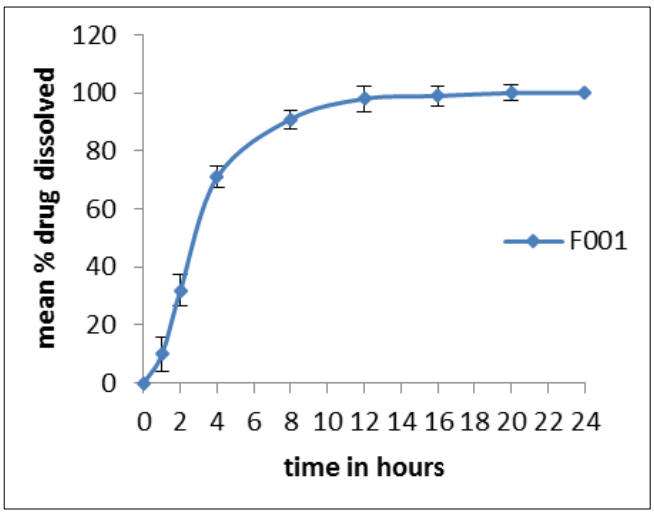

Fig 3: Dissolution profiles of F1

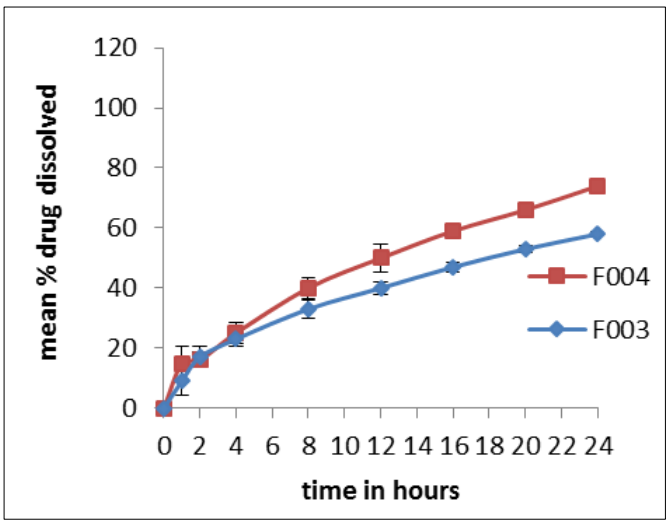

Fig 4: Dissolution profiles of F3,F4

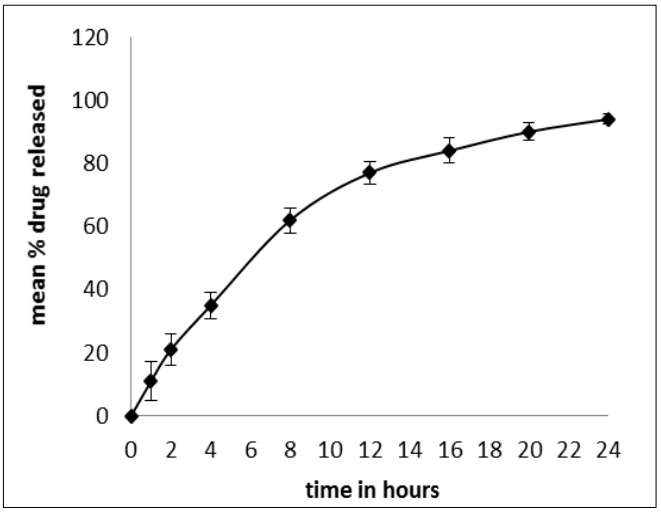

Fig 5: Dissolution profiles of F5

F1 was developed using Carbopol 974 NF as intragranular rate retarding polymer and Carbopol 971 NF as extragranular rate retarding polymer. F1 displayed excellent flow properties and compressibility. Dissolution profile of F1 displayed a rapid dissolution 98±1.5% drug release in 12 hours. In F002, extragranular carbopol 971 was replaced with Avicel 102, due to which the tablet disintegrates rapidly (within 10 min), and hence samples of this batch was not analyzed for dissolution profile Weight variation was not observed. When 30% of Methocel K4M was used as rate retarding polymer in F3, only 9% of the drug was released in first hour followed by 58% in 24 hours.It clearly suggests that the rate of hydration was very less which retards the swelling of polymer. Therefore, it was hypothesized that the use a combination of two different grades of Methocel as rate retarding polymer will produce the desired release profile. It was envisaged that a suitable combination of Methocel K4 M CR premium and Methocel E50 premium LV (low viscous) will give the desired drug release profile. In F4, 15% of Methocel K4M and 5% of Methocel E 50 LV was used as a rate retarding polymer and 74% of Cephalexin was released in 24 hours and significant (P>0.05) rise in rate dissolution was observed when compared with F3.

Table 10: Percentage cumulative drug release of F006, F007, F008 and F009

Time (hr)	Cumulative% drug release			
	F006	F007	F008	F009
1	24±6.2	20±5.6	20±5.6	20±6.0
2	30±4.5	27±4.2	28±5.0	26±5.1
4	41±3.5	40±4.6	42±4.9	43±3.2
8	53±3.0	58±3.9	61±4.0	63±.6
12	70±2.2	76±3.5	82±3.2	82±2.5
16	85±2.3	92±3.1	93±2.1	94±2.0
20	95±1.2	96±2.5	101±2.0	100±1.5
24	97±1.0	98±2.0	102±1.0	100±1.0

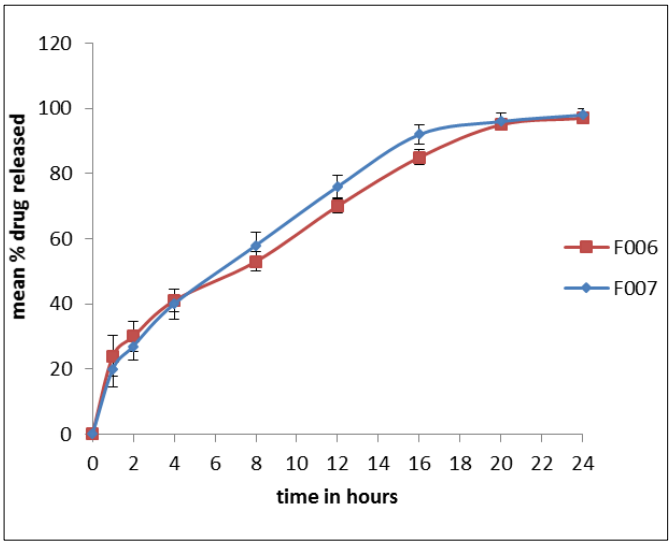

Fig 6: Dissolution profiles of F6 and F7

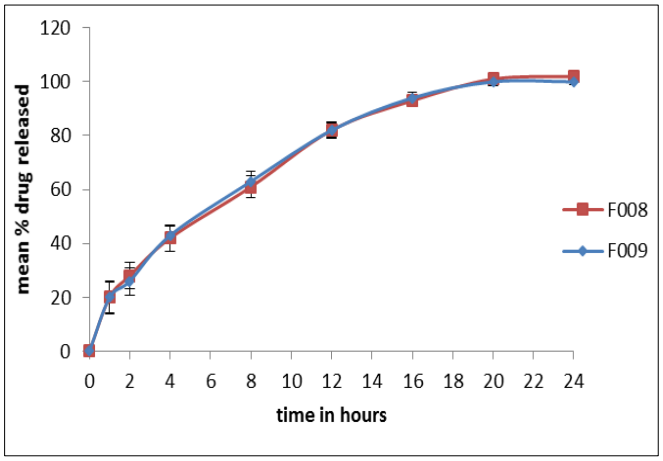

Fig 7: Dissolution profiles of F8 and F9

In F4, 15% of Methocel K4M and 5% of Methocel E 50 LV was used as a rate retarding polymer and it was observed that 74% of Cephalexin was released in 24 hours. Therefore it was decided to reduce the amount of Methocel K4M and in F006, 8% each of Methocel K4M and Methocel E 50LV was added as release rate retarding material and 0.5% of Methocel E 50LV as binder. As a result, a sharp significant (P>0.05) increase in dissolution rate was observed in F6, thereby releasing 97% of the drug in 20 hours. The Intra granular material of F006 was blended with the extra granular materials except Avicel PH 102 to a tablet weight of 1140mg, to ascertain the effect of extra granular MCC, and it was observed that though there is a drastic fall in compressibility of the blend but there was no significant difference in dissolution profile between F6 and F7. It was therefore concluded that extragranular MCC was necessary for proper compressibility and to attain the desired tablet hardness. Target was to get a drug release of 93-98% drug release in 16 hours. Hence, the quality of Methocel K4 MCR was further

lowered (5%) and Methocel E50 LV was increased (15%) in F8. It was observed that 93% of drug was released in 16 hours and 100% in 20 hours in F8.

Table 11: Cumulative% drug release of F10 and F11, F12, F13

Time (hr)	Cumulative% drug release			
	F10	F11	F12	F13
1	18±4.9	25±4.9	26±4.8	12±4.5
2	25±5.1	34±5.1	30±2.2	18±4.1
4	38±4.2	51±4.2	45±5.0	28±5.1
8	54±4.0	75±4.2	62±4.0	50±4.0
12	68±3.2	95±3.2	84±3.1	75±3.5
16	79±2.8	100±2.8	93±2.0	90±2.1
20	91±2.5	100±2.1	100±1.8	100±1.8
24	95±2.0	101±1.0	100±1.0	100±1.5

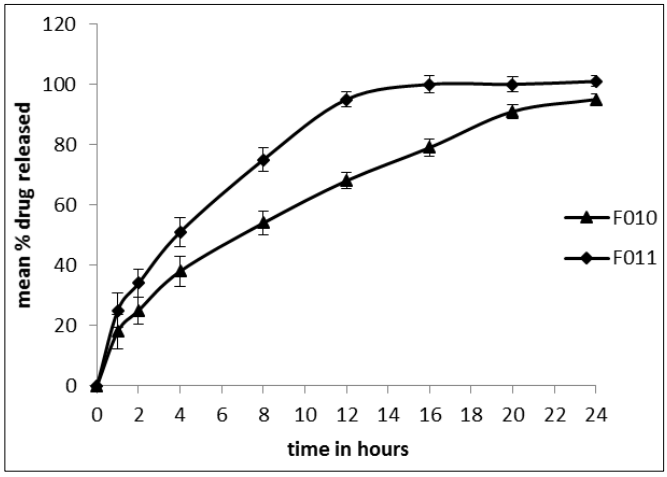

Fig 8: Dissolution profiles of F10and F11

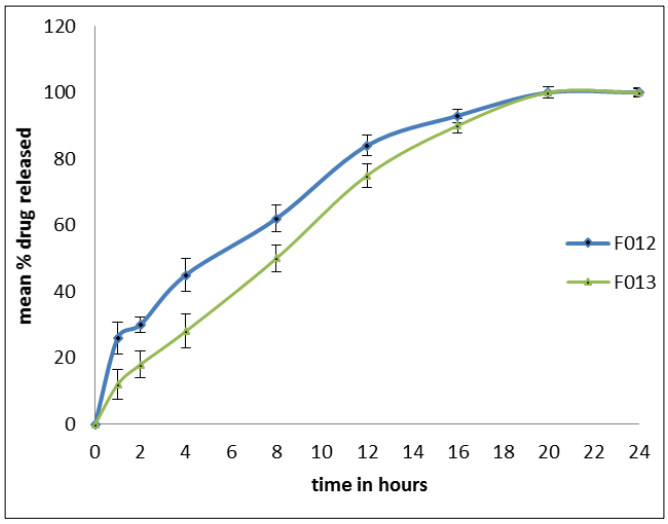

Fig 9: Dissolution profiles of F12 and F13

Increase in Methocel E 50 LV concentration from 0.5% in F8 to 1.0% in F10, leads to a significant drop (P>0.05) in dissolution rate. When water was used as a binder fluid in F11, the dissolution rate was drastically improved. This might be attributed to the poor strength of the granules and generation of fines during drying. It was therefore concluded that 0.5% of Methocel E 50 LV can be successfully used as binder solution. With 0.5% concentration of lubricant in F012, sticking and picking problems are observed during compression with rough surface of tablet. There is insignificant (P<0.001) difference in rate of% drug release. With 2.0% lubricant in F13 it was observed that shiny surface but decrease in hardness and decrease in% drug release when compared with the F8 (1.0%). Therefore, lubricant concentration (Magnesium stearate) was optimized at 1.0%.

Drug release kinetics of optimized formulation

Optimized formula F008 was selected to study different drug release kinetics to estimate the release mechanism.

Table 12: R^2 values of different kinetic models

Zero order release		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
R^2	*ko* (h^{-1})	R^2	k_H ($h^{-1/2}$)	R^2	*n value*	R^2	k_{HC} ($h^{-1/3}$)
0.913	4.126	0.990	22.50	0.662	0.950	0.929	0.244

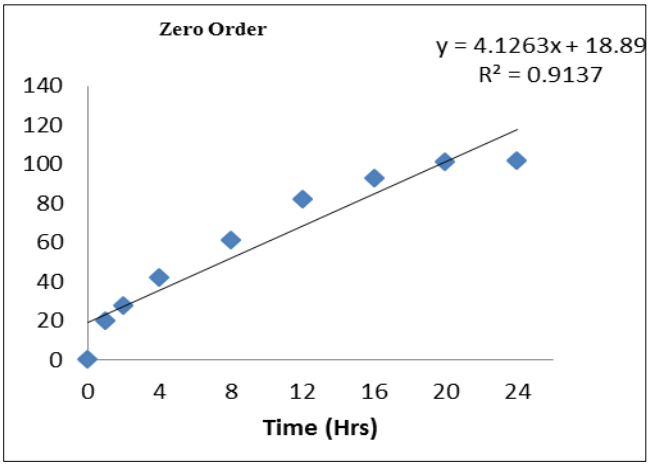

Fig 10: Zero Order kinetic profile of F008

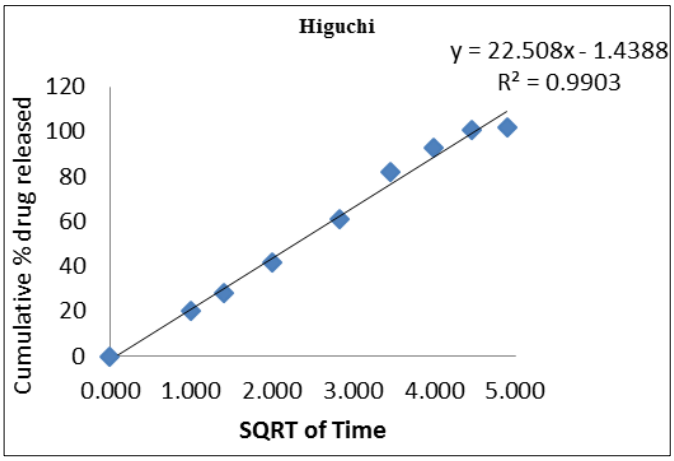

Fig 11: Higuchi plot of F008

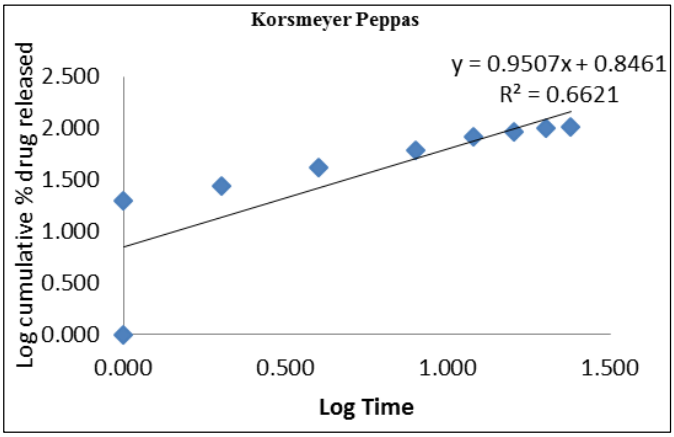

Fig 12: Korsmeyer Peppas plot of F008

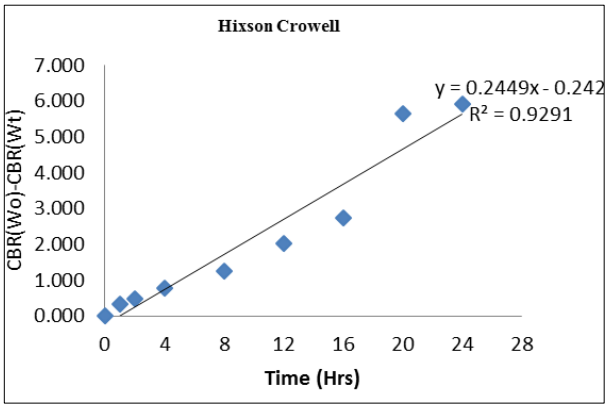

Fig 13: Hixson Crowell plot of F008

The straight line of linear regression analysis indicates zero order of the data yields the equation of best line with R^2 value 0.913 and the slope of line corresponds to the zero order rate constant was 4.126. The best linearity was found in Higuchi's equation plot (R^2=0.990) indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion. The dissolution data was also plotted in accordance with Hixson Crowell cube root law. Applicability of data (R^2 = 0.929) indicates a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time.

Conclusion

According to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. The value of the release exponent in Cephalexin controlled release obtained as 0.950 which is beyond the limits of Korsmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion controlled drug release mechanism, this is not automatically valid for HPMC [3].

An efficient extended release formulation of Cephalexin was designed to provide 24 drug release profile. For this, preformulation studies were conducted and analytical method was developed successfully. From the Drug–Excipient compatibility studies data, it is clear that Cephalexin is physical compatible with all the excipients except Myrj S 52. Based on the different strategies and trials it was optimized that the use of combination of two Methocel polymer grades to achieve desirable hydration of polymer as well as swelling to release drug in controlled manner. Dissolution profile of different formulation shows that the rate of drug release for Cephalexin from a hydrophilic matrix tablets is controlled by the polymer composition of matrix, higher the polymer concentration slower the drug release. By judiciously varying the ratio of drug to polymer, the desire matrix characteristics can be obtained to control initial burst and modulate drug release. F008 formulation was concluded as optimized formula based on the drug release profile and other evaluation parameters. F008 was developed by using Methocel K4M (5%) and Methocel E 50 LV (15%) as a rate retarding polymers.

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