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LITERATURE SURVEY
For many decades now, the conventional drug delivery systems i.e. tablets, capsules, pills, suppositories, creams, ointments, liquids aerosols, injectables are the primary pharmaceutical products commonly seen in the prescription and OTC products which provide prompt release of the drug to achieve and maintain the drug concentration within therapeutic range needed for treatment. Several potential problems are associated with this approach:

a) Unless the dosing interval is relatively short, depending on the biological half life of the drug, large peaks and valleys in the drug level occur. Oscillations in drug levels may be understandable in some diseased conditions.

b) Success by this approach is dependent on patient compliance with the dosing regimen. Numerous studies have documented that lack of compliance is an important reason for drug therapy inefficiency or failure.

c) During the early periods of dosing there may be insufficient drug to generate a favorable biological response, which may be a significant problem in certain diseased states.

d) For drugs with short biological half-lives, frequent dosing is needed to maintain relatively constant therapeutic levels of the drug.
It is often necessary to take this type of drug delivery system several times a day resulting in significant fluctuation in the drug plasma level. Recently, several technical advancements have been made which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue. These advancements have led to the development of several novel drug delivery systems that have revolutionized the method of medication and provide the following therapeutic benefits:

a) Better patient compliance/convenience

Table 2.1: Frequency of dosing Vs % compliance

<table>
<thead>
<tr>
<th>FREQUENCY OF DOSING</th>
<th>PERCENT COMPLIANCE (All medication taken as directed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o.d.</td>
<td>90 %</td>
</tr>
<tr>
<td>b.i.d.</td>
<td>69 %</td>
</tr>
<tr>
<td>t.i.d.</td>
<td>38 %</td>
</tr>
</tbody>
</table>

b) Employ less total drug

- Minimize or eliminate local side effects
- Minimize or eliminate systemic side effects
- Obtain less potentiation or reduction in drug activity with chronic use
- Minimize drug accumulation with chronic dosing

c) Improve efficiency in treatment

- Cure or control condition more promptly
- Improve control of condition i.e. reduce fluctuation in drug level
- Make use of special effect e.g. sustained release aspirin provides sufficient drug, so that on awakening the arthritic patient has symptomatic relief

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Oral controlled release drug delivery systems (OCRS)\textsuperscript{8,9}

Oral route is the most widely utilized route of administration for systemic delivery of drugs in various pharmaceutical dosage forms. In general sense, the gastrointestinal tract is a hostile environment which must be contended within product design. The oral route is a relatively safe route for sustained release drug delivery and offers less potential dangers than any other routes. Thus although the constraints of the oral route are numerous, and at times severe, there is still more flexibility in dosage form design, by this route, than exists for other routes.

All the pharmaceutical products formulated for systemic delivery, via the oral route of administration, irrespective of mode of delivery, (immediate, sustained, or controlled release) and the design of dosage form (either solid, dispersion or liquid) must be developed within the intrinsic characteristic of G.I. physiology. Therefore the fundamental understanding of various disciplines including G.I. physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systematic approach to the successful development of an oral pharmaceutical dosage form. Although it is often impractical to alter the physicochemical, pharmacokinetic and pharmacodynamic characteristics of a drug to be delivered by a chemical approach, such as synthesis of analog, or medically undesirable to modify the anatomic and physiological characteristic of the G.I.T., the design of controlled release of oral dosage form by optimization of dosage form characteristic with G.I. anatomy and physiology taken into consideration could provide some opportunity to rationalize systemic delivery of drugs and maximize their therapeutic benefits. Thus the controlled release drug administration means not only prolongation of drug delivery time but continuous delivery of drug at predictable and reproducible kinetics for a predetermined period throughout G.I. transit.
A review of the literature has revealed the following Novel Drug Delivery systems that can be utilized for the controlled delivery of drugs in the alimentary canal:

a) Dissolution controlled release systems
   i) Matrix (or monolithic) dissolution controlled release
   ii) Encapsulation / coating dissolution controlled system (Reservoir devices)

b) Diffusion controlled release systems
   - Matrix diffusion controlled system
     i) Non-swellable hydrophobic matrix (rigid matrix)
     ii) Swellable hydrophilic substance
   - Reservoir devices (or Laminated devices)

c) Dissolution and diffusion controlled release systems
d) Osmotic pressure – controlled gastrointestinal delivery systems e.g. Acutrim tablets achieve 16 hrs oral controlled delivery of Phenyl propanolamine
e) Hydrodynamic pressure – controlled gastric intestinal delivery systems
f) Membrane permeation controlled gastrointestinal delivery systems
   - Micro porous membrane permeation controlled gastrointestinal delivery systems
   - Gastric fluid resistant intestine targeted controlled release delivery systems

g) Gel diffusion intestine targeted controlled release delivery systems
h) pH controlled intestine targeted controlled release delivery systems
i) Ion exchange intestine targeted controlled release delivery systems e.g. Pennkinetic system (Pennwest Pharmaceuticals) (sustained release suspension)
Prolongation of G.I. retention
i) Hydrodynamically balanced intragastric delivery systems
ii) Intragastric floating gastrointestinal drug delivery systems
iii) Inflatable gastrointestinal controlled drug delivery systems
iv) Ingestic osmotically controlled drug delivery systems
v) Intrarumen controlled drug delivery systems
vi) Bio(muco)adhesive controlled delivery systems
vii) Co-administration with GI motility reducing drugs

k) Overcoming hepatic first pass metabolism
i) Oral mucosal drug delivery
ii) Rectal mucosal drug delivery

Because of their relative ease of production and cost, compared with other methods of sustained or controlled delivery, dissolution and diffusion-controlled systems have classically been of primary importance in oral delivery of medication.

2.1.1 Matrix diffusion controlled systems

A matrix device consists of drug dispersed homogeneously throughout a polymer matrix. The drug in the outside layer exposed to the dissolution medium is dissolved first and then diffuses out of the matrix. The process continues with the interface between the dissolution medium and the solid drug moving toward the interior. For this system to be diffusion-controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Matrix systems offer several advantages. They are, in general, easy to make. Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release. The primary disadvantages of this system are that the remaining
matrix ghost must be removed after the drug is released. Also, the release rates generated are not zero-order, since the rate varies with the square root of time. A substantial sustained effect however can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order. A list of matrix diffusional products is shown in table 2.2 below:

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug substance</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desoxyn-Gradumet</td>
<td>Methamphetamine hydrochloride</td>
<td>Abbot</td>
</tr>
<tr>
<td>Fer-Gradumet</td>
<td>Ferrous sulphate</td>
<td>Abbot</td>
</tr>
<tr>
<td>Tral Filmtab</td>
<td>Hexocyclium methylsulfate</td>
<td>Abbot</td>
</tr>
<tr>
<td>PBZ-SR</td>
<td>Tripelemamine</td>
<td>Geigy</td>
</tr>
<tr>
<td>Procan SR</td>
<td>Procainamide hydrochloride</td>
<td>Parke-Davis</td>
</tr>
</tbody>
</table>

Matrix diffusion controlled systems are classified into two types:¹¹

a) Non swellable matrix: where the drug is dispersed in an insoluble matrix of rigid nonswellable hydrophobic material such as PVC, fatty materials like Stearic acid and Bees wax.

b) Swellable hydrophilic matrix: These systems are popular for sustaining highly water soluble drugs. The materials used for such matrix are generally hydrophilic gums such as Guar gum and Tragacanth of natural origin, Hydroxypropyl Methylcellulose (HPMC), Carboxymethyl cellulose (CMC) and Xanthan gum of semi-synthetic origin and polyacrylamide of synthetic origin. The release of drug from such initially dehydrated hydrogels involves simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug via a swelling controlled diffusion mechanism. As the gum swells and the drug diffuses out of it, the swollen mass, devoid of drug appears transparent or glasslike and therefore the system is sometimes called as glass hydrogel.
In such systems, the dissolution medium surrounding the controlled release device may enter the polymer at a rate that controls the drug release. The drug release follows the (case I) Fickain first order diffusion under equilibration condition. This case I transport is described by a diffusion coefficient where release mechanism of drug from swellable polymer matrix is governed by the diffusion process.

The fractional drug release by this mechanism from the slab is given by equation:

\[
\frac{Mt}{M\infty} = 4 \frac{Dt}{\pi l^2}^{1/2}
\]

Where

\( \frac{Mt}{M\infty} \) = fraction drug released

\( D \) = Diffusion coefficient

\( l \) = Initial film thickness

\( t \) = Release time

The Fickian release indicates that the fractional drug release at any time is characterized by the constant multiplied by the square root of time.

Further, the release of drug through the swelling controlled release system taken by case II transport is described by a characteristic relaxation constant. The release kinetics is assumed to be controlled by a rate limiting relaxation phenomenon positioned at the advancing front which also follows first order kinetics:

\[
\frac{Mt}{M\infty} = 2K_0\frac{1}{C_0l}t
\]

The case II transport indicates that until the two penetration fronts meet, the fractional release at any time is linearly related to time.
Under certain conditions, zero order release can be achieved where the prevailing molecular mechanism is a coupling of diffusion and macromolecular relaxation as a result of which the drug diffuses outward with a kinetic behavior that is dependant on the relative ratio of diffusion and relaxation called as Anomalous behavior or non-Fickian behavior which is intermediate between Fickian and case II given by equation:

\[ M_t = K_1 \sqrt{t} + K_2 t \]

\[ M_\infty \]

The generalized expression for the previous equations is

\[ M_t = K t^n \]

\[ M_\infty \]

where K (constant) is characteristic of the macromolecular network system and the drug , whereas diffusional exponent, n, is indicative of the transport mechanism. Fickain and case II release are defined by n equal to 0.50 and 1.00 respectively and Anomalous behavior is defined by value between 0.5 and 1.0.

### 2.1.2 Development criteria for design of OCRS

The basic considerations in designing of oral controlled release systems are:

a) Drug Candidate

b) Polymer system

c) Delivery system
2.1 Drug Candidate

The type of delivery system in oral controlled release dosage forms depends upon the physicochemical properties of the drug and its biopharmaceutics characteristics as given below:

a) Molecular weight of the drug: The lower the molecular weight, the faster and more complete the absorption. For drugs absorbed by pore transport mechanism, the molecular size threshold is 150 daltons for spherical compounds and 400 daltons for linear compounds. However, more than 95% of drugs are absorbed by passive diffusion. Diffusivity, defined as the ability of drug to diffuse through the membrane, is inversely related to the molecular size. The upper limit of drug molecular size is 600 daltons. Drugs with large molecular size are poor candidates for OCRS e.g. peptides and proteins.

b) Aqueous solubility of the drug: A drug with good aqueous solubility, especially if pH-independent, serves as a good candidate for controlled release dosage forms. Drugs with pH dependent aqueous solubility and drugs with poor aqueous solubility are not good candidates for OCRS. Absorption of poorly soluble drugs is dissolution rate-limited which means that the controlled release device does not control the absorption process; hence, they are poor candidates for such systems.

c) Apparent partition coefficient of the drug: Greater the apparent partition coefficient of a drug, greater is its rate and extent of absorption. Such drugs have increased tendency to cross even the more selective barriers like BBB. The apparent volume of distribution of such drugs also increases due to increased partitioning into the fatty tissues and since the blood flow rate to such tissues is always lower than that to an aqueous tissue like liver, they may exhibit characteristics of models having two or more compartments. The parameter is also important in determining the release rate of a drug from lipophillic matrix or device.

d) Drug pKa and ionization at physiologic pH: The pKa range for acidic drugs whose ionization is pH-sensitive is 3.0 to 7.5 and that for basic drugs is 7.0 to 11.0. For optimum
sive absorption, the drugs should be in non-ionized form at the site at least to an extent of 0 to 5%. Drugs existing largely in ionized forms are poor candidates for controlled delivery e.g. hexamethonium.

d) Drug stability: Drugs unstable in GI environment cannot be administered as oral controlled release formulation because of bioavailability problems e.g. nitroglycerine. A different route of administration should then be selected such as the transdermal route.

e) Mechanism and Site of Absorption: Drugs absorbed by carrier-mediated transport processes and those absorbed through a window are poor candidates for controlled release systems e.g. several B vitamins.

f) Biopharmaceutic Aspects of Route of Administration: For a drug to be successful as oral controlled release formulation, it must get absorbed through the entire length of G.I.T. Since the main limitation of this route is the transit time (a mean of 14 hours), the duration of action can be extended for 12 to 24 hours. The route is suitable for drugs given in dose as high as 1000 mg. A drug whose absorption is pH dependent, destabilized by GI fluids/enzymes, undergoes extensive presystemic metabolism (e.g. nitroglycerine), influenced by gut motility, has an absorption window and/or absorbed actively (e.g. riboflavin), is a poor candidate for oral controlled release formulation.

g) Absorption Rate: For a drug to be administered as controlled release formulation, its absorption must be efficient since the desired rate-limiting step is rate of drug release Kr i.e. Kr <<Ka. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug e.g. iron. Aqueous soluble but poorly absorbed potent drugs like decamethonium are also unsuitable candidates since a slight variation in the absorption may precipitate potential toxicity.

h) Elimination Half-Life: Smaller the t1/2, larger the amount of drug to be incorporated in the controlled release dosage form. For drugs with t1/2 less than 2 hours, a very large dose may be required to maintain the high release rate. Drugs with half-life in the range 2 to 4 hours make good candidates for such a system e.g. propranolol. Drugs with long half-life need not be
Presented in such a formulation e.g. amlodipine. For some drugs e.g. MAO inhibitors, the duration of action is longer than that predicted by their half-lives. A candidate drug must have $t\frac{1}{2}$ that can be correlated with its pharmacologic response.

i) Rate of Metabolism: A drug which is extensively metabolized is suitable for controlled release system as long as the rate of metabolism is not too rapid. The extent of metabolism should be identical and predictable when the drug is administered by different routes. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood levels would be difficult to maintain.

j) Dosage Form Index (DI): It is defined as the ratio of $C_{ss\text{,max}}$ to $C_{ss\text{,min}}$. Since the goal of controlled release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible.

k) Therapeutic Range: A candidate drug for controlled delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.

l) Therapeutic Index (TI): The release rate of a drug with narrow-therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range. This is necessary because such drugs have toxic concentration nearer to their therapeutic range. Precise control of release rate of a potent drug with narrow margin of safety is difficult. A drug with short half-life and narrow therapeutic index should be administered more frequently than twice a day. One must also consider the activity of drug metabolites since controlled delivery system controls only the release of parent drug but not its metabolite.

m) Plasma Concentration-Response Relationship: Drugs such as reserpine whose pharmacologic activity is independent of its concentration are poor candidates for controlled release systems.
2 Polymer system

Since the required input in terms of time, money and manpower is tremendous in the development of a new drug molecule, the focus of pharma technology, is now mainly on modifying the delivery of the existing drugs. This effort is exemplified in the designing of sustained release dosage forms which aim at spatial as well as temporal delivery of drugs at a considerably lower cost. Polymers have played an important role in man's endeavor in development of such systems so it is very essential to study the various properties of polymers which in turn affect the release of drug from such formulations. These properties are as follows:

a) Porosity: Cross linking of polymeric chains affect the permeability. Higher degree of cross-linking reduces the permeability, when active agents are dispersed in polymers. The geometry plays an important role when one considers tortuosity, the pores present are assumed to form uniform cross connections. Hence the molecules have to travel a greater distance than if the pores were straight. In case of corrugation model, one assumes that there are places where the pores tend to be narrower. This geometry closely approximate porous polymers. The arrangement of pores can also affect the release. The pores may be isolated or interconnected. As porosity increases, the pores become inter-connected consequently increasing the availability of the active ingredient. For two dimensional matrix this increase is about 50-70% & for 3 dimensional it is about 20-43%.

Porosity can be achieved by variation in a fabrication procedure, relative leaching of soluble components (polymer blends or volatile diluents or plasticizer) or by careful micro-deformation of certain crystalline or glassy polymers. The swelling of polymer under applied environmental conditions increase porosity and hence release rate.

b) Hydrophillicity of the polymer: Hydrophilic polymers, which swell in presence of water, offer the best choice to modify the release rate of drug. Due to swelling, the distance to be traveled by the core drug before it encounters body fluid increases whereas the drug at the surface is immediately absorbed. This can be seen from table 2.3:
Table 2.3: Parameters affecting drug release from hydrophilic polymers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Diff. Coeff. cm²/sec</th>
<th>Partition coeff. polymer / water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetophenone</td>
<td>Polyethylene</td>
<td>3.5 x 10⁻⁸</td>
<td>3.16</td>
</tr>
<tr>
<td>Chlormadinone acetate</td>
<td>Silicone rubber</td>
<td>3.03 x 10⁻⁷</td>
<td>82</td>
</tr>
<tr>
<td>Estriol</td>
<td>Polyurethane ether</td>
<td>2 x 10⁻⁹</td>
<td>133</td>
</tr>
</tbody>
</table>

c) Mobility of segments: Diffusion coefficient depends on mobility of polymer chain segments. Diffusion of a molecule in a polymer requires the co-operative movements of several polymeric chain segments. This is why the drugs have higher diffusion coefficient in polymers that have lower inter-chain forces such as silicone rubber and natural rubbers as compared with polystyrene. The local segmental mobility may be affected by chain interactions arising from hydrogen bonding, polar group interactions or simple Van der Waal's attraction. As the number of these grouping per unit chain segment length increases, the degree of interaction increases, the segmental mobility decreases and the permeation rate also decreases. These effects are especially pronounced in the case of symmetrical substitution of polar groups, since the packing of adjacent chain segment is somewhat facilitated leading to more effective interactions.

d) Nature of grafted polymer: The dependence of polymer membrane permeation properties on the nature of grafted polymer chain length, conformation and domain formation have been elucidated by using several membrane materials which were subjected to controlled graft co-polymerization procedure. The improved permeation barrier characteristics of poly (isoprene-g-methyl methacrylate) to inert gas reentrants were found for short chain or densified graft domains as compared with long chain or extended domains. It is also reported that the presence of short graft chains act as relatively inert fillers or excluded volume by chain packing effect, more effectively than does longer graft chains. The short chains are
considered to be distributed along the backbone chain allowing a more effective packing and structured densification than do the relatively isolated comparatively long chain domains.

c) Wettability: If liquid can wet (i.e. contact angle below 90°) the penetration takes place basically via capillary motion through pores. Pore size, volume, surface tension of liquid and its viscosity affect the penetration. If the liquid cannot wet the polymer (contact angle above 90°), release can take place only by dissolution of the drug particles or by permeation of the polymeric particles themselves. In this case, the basic factors controlling the diffusion of the liquid movement through the polymer are cross-linking, density and crystallinity of the polymer.

The pore volume may not be significantly affected with change in wettability. As wettability decreases, drug release rate decreases. This means that in the case of hydrophobic polymers (e.g. polyethylene) the pore network cannot be penetrated by capillarity, so that pore volume effectively available for drug diffusion is only that left by the already dissolved drug particles.

Table 2.4: Wettability and drug release rate

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Pore volume</th>
<th>Contact angle</th>
<th>Aspirin release rate mg/cm²/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylate</td>
<td>0.18</td>
<td>51° 01’</td>
<td>0.16</td>
</tr>
<tr>
<td>PVC-PTFE</td>
<td>0.12</td>
<td>100°01’</td>
<td>0.1</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>0.13</td>
<td>95° 58’</td>
<td>0.02</td>
</tr>
</tbody>
</table>

For wettable polymers like acrylates, decrease in pore volume caused by any process like sintering, brings a corresponding decrease of the volume generated by capillarity and hence the volume available effectively for drug diffusion is reduced and drug release rate is slowed down.
Table 2.5: Effect of sintering time of polymer on release rate of drug

<table>
<thead>
<tr>
<th>Sintering time</th>
<th>Pore volume m/g</th>
<th>Water penetration</th>
<th>Aspirin release rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.176</td>
<td>0.167</td>
<td>0.073</td>
</tr>
<tr>
<td>0.5</td>
<td>0.169</td>
<td>0.104</td>
<td>0.033</td>
</tr>
<tr>
<td>1-5</td>
<td>0.139</td>
<td>0.077</td>
<td>0.018</td>
</tr>
</tbody>
</table>

f) Excipients added during processing: During the processing of polymers, various excipients like fillers, plasticizers etc. are added to facilitate the polymerization process. These excipients can also alter the release rates of the drug. Plasticizers increase the permeability of polymers. Fillers, usually of inorganic origin, decrease the permeability. However, the effect is complicated by type, shape and amount of filler and its interaction with the polymer.

g) Crystallinity: Maximum interchain attraction, resulting in greatest mechanical strength, requires that the polymer chains be packed as densely as possible and that the polar groups of adjacent chains be in registry, so that there is an efficient geometric matching-up of interacting dipoles or hydrogen-bonding groups between the chains. As crystallinity increases, the segmental mobility of the polymeric chains decreases with subsequent reduction in the release rate.

h) Glass transition temperature: It is the temperature at which the phase transition of polymer from glassy to rubbery or vice-versa takes place. The lower the Tg, higher is the permeability for a given type of polymer. Rubbery polymers have high permeability but occasionally lack mechanical strength and must be reinforced by cross-linking. Lower the Tg, greater is the release of active ingredient.

i) Hydrophobicity of a polymer: The greater the uptake of water and the lower the Tg, of hydrophobic polymers, the greater is the release rate. The release from hydrophobic polymers also depends upon crystallinity, fillers, plasticizers, electrolyte addition etc.
2.3 Delivery system

The various systems utilized for the controlled delivery of drugs in the alimentary canal are already discussed in 2.1.

2.1.3 Application of OCRS to antibiotics

The major parameters used to quantify the effect of antimicrobial drugs are the minimum inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC). Although these parameters are good predictors of the potency of the drug-microorganism interaction, they do not provide any information on the kinetics of drug action. For instance, the MBC value does not provide information on the rate of bactericidal activity and whether this rate can be enhanced by increasing antimicrobial concentrations. Similarly, the MIC does not provide any information about the persistent activity of the antimicrobial agent that remains following exposure to the drug.

Antibiotics can be divided into 3 categories based on their pharmacodynamic properties, including both their bactericidal activity and their persistent effects\textsuperscript{13}:

2.1.3.1 Category I exhibits time dependent killing rather than concentration-dependent killing and produces short-term or persistent effect with most bacteria. The killing rate of these antibiotics saturates at concentrations of around 4-5 times the MBC. Thus, high concentrations will not kill bacteria faster than lower concentrations. Furthermore, bacterial regrowth starts soon after serum and tissue concentrations fall below MIC. Penicillins, cephalosporins and aztreonam exhibit this time course of antimicrobial activity.

\textit{In vitro} studies of the pharmacodynamics of \(\beta\)-lactam antibiotics have shown that killing of bacteria, in particular gram-negative aerobic rods, is slow, time dependent and maximal at relatively low concentrations\textsuperscript{14}. Further, elevation of the dose is not associated with increased bactericidal potency\textsuperscript{15,16}. It has also been suggested that at concentrations much greater than the MIC, a paradoxical pattern may occur, i.e., a decrease in bacterial kill potency\textsuperscript{17}. These findings have led to the hypothesis that continuously maintained concentrations above a
Efficacy studies in laboratory animals are in agreement with these in vitro findings. It was found that in order to obtain the same efficacy, the daily doses have to be 8-fold higher during intermittent infusion regimens than during continuous infusion\textsuperscript{15}. Other studies have shown that the percentage of survival of the animals increased linearly with the frequency of dosing and time over the MIC but not with other pharmacodynamic parameters\textsuperscript{18}.

In addition to the pre-clinical findings, several clinical efficacy studies corroborate this concept, however, these are still scarce. Schentag et al. have shown a significant relationship between time to eradication of gram-negative pneumonia and time over MIC\textsuperscript{19}. Weinstein et al. examined the relationship between \(\beta\)-lactam concentrations at trough and the success of therapy in patients with acute and chronic osteomyelitis\textsuperscript{20}.

It was found that maximum efficacy with \(\beta\)-lactam antibiotics in humans appeared to be dependent on maintaining levels above the MIC of the infecting organism for the majority of the dosage interval. The few randomized trials that have compared the efficacy of the \(\beta\)-lactams given by continuous vs. intermittent administrations also support this conclusion.

Exposures of staphylococci, streptococci, or enterococci to different \(\beta\)-lactams are consistently followed by post anti-biotic effects (PAEs) of several hours' duration\textsuperscript{15}.

This persistent suppression of gram-positive cocci growth enabled the development of intermittent dosing regimens for these drugs. Traditionally, intermittent intravenous infusions or intramuscular injections have been considered optimal dosing regimens that worked reasonably well in clinical practice. However, because of the increasing number of immuno-compromised patients, the rising incidence of gram-negative infections, and the availability of improved intravenous drug delivery systems, new strategies have been introduced for improving antimicrobial therapy with \(\beta\)-lactams. These strategies apply continuous infusions of these drugs to provide improved patient outcome with reduced doses of drug\textsuperscript{16}. In summary, the goal of the dosage regimen of \(\beta\)-lactam drugs should be to prevent the drug-free interval doses from being long enough for the bacterial pathogen to resume growth.

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3.1.1 Target therapeutic concentration\textsuperscript{18}

Several investigators have proposed, based on \textit{in vitro} experiments, that a maximum effect is reached at 4 x MIC for the target bacterium.

Preclinical investigators clarified that the target therapeutic concentration depends on the status of the immune system. For example, serum ceftazidime concentration needed during continuous infusion to obtain 50\% efficacy in normal rats was between 1/6 and 1/5 the MIC, for the infecting \textit{K. pneumonia}, depending on the severity of the infection. However, the concentration needed to obtain 100\% efficacy (ED\textsubscript{100}) was dependent not only on the severity of infection but also whether the animals were leukopenic or not.

2.1.3.1.2 Required time over MIC (T>MIC)\textsuperscript{21,22,23}

Craig has summarized all the available data from the literature that use mortality as an endpoint and in which animals infected with \textit{S. pneumoniae} were treated with penicillins or cephalosporins. The duration of time that the serum level needs to be above the MIC to ensure efficacy was determined in one study. Mortality was virtually 100\% if serum levels were above MIC for 20\% or less of the dosing interval. In contrast, as soon as T > MIC was 40-50\% of the dosing intervals or higher, bacteriologic efficacy was 90-100\%. Similar results were found in clinical studies that assessed bacteriologic cure in \textit{Otitis media}. The findings indicate that if serum levels are above the MIC for 40-50\% of the dosing interval, a bacteriologic cure of over 90\% is obtained. In some \textit{\beta}-lactum antibiotics, a T>MIC of 30\% is also effective eg Amoxycillin.

The above approaches have been used to extend the activity of amoxycillin, a \textit{\beta}-lactum, which has pharmacokinetic properties similar to other drugs from this category, including short elimination half-life and active absorption limited to the upper parts of the G.I. tract\textsuperscript{24}.

Prolongation of T>MIC for these drugs following oral administration is limited by the narrow absorption window. To overcome this pharmacokinetic limitation, the controlled release matrix tablet was designed, in the reported study, to release 50\% of its content within 3 hours,
allowed by a constant release rate for about 8 hours. The rapid onset of drug release was
designed to provide an initial ‘loading dose’ and to maximize the absorption phase in those
parts of the intestine in which amoxicillin is actively absorbed by a carrier-mediated process.
The *in vivo* evaluation of this formulation revealed that the extent of absorption of the new
formulation was not much different than that of a regular soft gelatin capsule formulation.
Furthermore, the time required to obtain therapeutic concentration (onset time) was found to
be identical for the two formulations. However, T>MIC and T>4 x MIC of the drug against
susceptible pathogens was found to be maintained for a significantly longer period.
The following equation can be used to calculate T>MIC:

\[
T\text{>MIC(\%)} = \frac{T\text{>MIC} \times 100}{\text{Dosing interval (Hrs.)}}
\]

2.1.3.2 Category II is characterized by concentration dependent killing over a wide range
of concentrations and by prolonged persistent effects. The higher the drug concentration, the
greater the rate and extent of bacterial killing. This category includes aminoglycosides,
fluoroquinolones and metronidazole. The 24hour AUC>MIC ratio is the parameter that best
co-relates with the efficacy of fluoroquinolones. When tested for ciprofloxacin, this parameter
was better than the peak drug concentration and considerably better than T>MIC needed to
exceed the MIC for about 20% of the time interval to obtain any bacterial killing. This
rationale was used for developing once a day formulation of Ciprofloxacin, vide US patent
6,261,601, by Ranbaxy Research Laboratories, India.

2.1.3.3 Category III contains drugs such as clindamycin and macrolides such as
clarithromycin and azithromycin, which demonstrate minimal concentration dependent killing
but have prolonged persisting effects. Abbot has launched once a day tablets of clarithromycin
(Biaxin XL) which have been proved to provide equivalent drug absorption as compared to
the original twice-daily formulation.
4.4 Use of Probenecid

Many drugs and drug metabolites are actively secreted by the proximal tubular active transport mechanism and interactions may arise from competition for these systems. Particularly with antibiotic therapy, active tubular secretion is a significant route of elimination. Drugs that use the same active transport system in the kidney tubules can compete with one another for secretion. Probenecid may be used as an adjunct to antibacterial therapy particularly when treating severe or resistant infections. It reduces the tubular excretion of penicillins and most cephalosporins and may increase their plasma concentrations up to fourfold. The usual dosage for reducing tubular excretion of penicillins and cephalosporins is 500mg four times daily. Single doses of probenecid 1g are given together with an oral antibacterial or at least 30 minutes before an injected antibacterial, in single-dose treatment of gonorrhoea.

2.2 Requirements of PK studies

Bioavailability is defined as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action. From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the BA data for a solution, suspension or intravenous dosage form. BA for orally administered drug products can be documented by developing a systemic exposure profile obtained from measuring the concentration of active ingredients over time in samples collected from the systemic circulation. Systemic exposure patterns reflect both release of the drug substance from the drug product and a series of possible presystemic/systemic actions on the drug substance after its release from the drug product. The regulatory objective is to assess, through appropriately designed BA studies, the performance of the formulations used in the clinical trials that provide evidence of safety and efficacy.
The first modified-release drug product for a previously approved immediate-release product is prepared the purpose of an *in vivo* BA study is to determine if all of the following conditions are met:

- the drug product meets the controlled release claims made for it
- the BA profile established for the drug product rules out the occurrence of any dose dumping
- the drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled release drug product that contains the same active drug ingredient
- the drug product's formulation provides consistent pharmacokinetic performance between individual dosage units

The reference material for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled release claims made for the drug product such as:

- a solution or suspension of the active drug ingredient
- a currently marketed noncontrolled-release drug product containing the same active drug ingredient and administered according to the dosage recommendations in the labeling
- a currently marketed controlled-release drug product containing the same active drug ingredient and administered according to the dosage recommendations in the labeling

**Bioequivalence** (BE) is defined as the absence of a significant difference in the rate and extent to which the active ingredient in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

For a modified release product which is already marketed, only BE studies are required to be performed. Such BE studies should include:

- a single-dose nonreplicate, fasting study comparing the highest strength of the test and reference listed drug product
A food-effect, nonreplicate study comparing the highest strength of the test and reference product. Because single-dose studies are considered more sensitive in addressing the primary question of BE, multiple-dose studies are generally not recommended even in instances where nonlinear kinetics are present. The following pharmacokinetic information is to be derived for BA/BE studies:

- plasma concentrations and time points
- subject, period, sequence, treatment
- AUC$_{0-\infty}$, C$_{max}$, T$_{max}$, $\lambda$ and $t_{1/2}$

In addition the following statistical information should be provided for AUC$_{0-\infty}$ and C$_{max}$:

- Geometric mean
- Arithmetic mean
- Ratio of means
- Confidence intervals

Log transformation should be provided for measures used for BE demonstration.

2.3 Patent search

The relevant prior art methods, used for extending the release of some $\beta$-lactam antibiotics are as follows:

U.S. Pat. No. 4,250,166 discloses a long-acting cephalxin preparation comprising of normal quick-releasing cephalxin and particulate cephalxin coated with a copolymer of methylmethacrylate and methacrylic acid which dissolves at a pH from 5.5 to 6.5 and the potency ratio of the normal cephalxin to coated cephalxin is between 40:60 and 25:75.

U.S. Pat. No. 4,713,247 discloses a long-acting cefaclor formulation comprising of a mixture of non-enteric coated rapid-release cefaclor component and an enteric coated slow-release cefaclor component at a ratio of 4:6 based upon cefaclor potency, wherein the rapid-release
ponent releases the drug in gastric fluid while the slow-release component dissolves at pH 5.8, thereby enabling oral administration thereof twice a day.

J.S. Pat. No. 4,968,508 discloses a sustained release matrix tablet comprising from about 0.1 % to about 90 % by weight of cefaclor, about 5 % to about 29 % by weight of hydrophilic polymer and about 0.5 % to about 25 % by weight of an acrylic polymer which dissolves at a pH in the range of about 5.0 to about 7.4, the total weight of polymers being less than 30 % by weight of the formulation. Although a specific cefaclor formulation is claimed, the text suggests that the matrix formulation is suitable for weakly basic drugs and particularly suitable for cephalexin and cefaclor. A simulated gastrointestinal method has been used to evaluate the release profiles of the various compositions described. This method involves exposing the tablets for one hour to 0.1NHCl after which the pH in the dissolution kettle is increased to pH 6.8 by the addition of 250mL of 0.2M tribasic sodium phosphate. Some of the dissolution profiles obtained for 4-hours profile of cefaclor compositions, using the above method are disclosed in the patent as shown in Table 2.6:

<table>
<thead>
<tr>
<th>Time in minutes</th>
<th>Formula 1</th>
<th>Formula 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>60</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>90</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>120</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>180</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>240</td>
<td>100</td>
<td>99</td>
</tr>
</tbody>
</table>

U.S. Pat. No. 5,948,440 discloses a controlled release tablet of an active ingredient comprising of cefaclor, cephalexin, or their pharmaceutically acceptable hydrates, salts, or esters as active ingredient, and a mixture of hydrophilic polymers selected from the group consisting of at
least one hydroxypropyl methylcellulose and at least one hydroxypropylcellulose. The composition optionally also contains one or more of a water soluble or water dispersible diluent. The quantities of the hydrophilic polymers and water soluble or water dispersible diluent are such that the therapeutically effective active ingredient is released at a rate suitable for twice daily administration of the pharmaceutical composition. The patent also discloses the following dissolution method for in-vitro evaluation of the examples shown therein:

900mL of 0.1N HCl for one hour, after which the dissolution medium is changed to a pH 6.8 mixed phosphate buffer (900mL). Tablets are placed into a 40-mesh basket (USP Apparatus-Type -1) and rotated at 100rpm.

The dissolution profiles disclosed for compositions of cefaclor meant for BID application are shown in table 2.7:

<table>
<thead>
<tr>
<th>Time in minutes</th>
<th>Formula 1</th>
<th>Formula 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>43.46</td>
<td>50.83</td>
</tr>
<tr>
<td>120</td>
<td>69.06</td>
<td>80.06</td>
</tr>
<tr>
<td>180</td>
<td>88.91</td>
<td>100.61</td>
</tr>
<tr>
<td>240</td>
<td>101.53</td>
<td></td>
</tr>
</tbody>
</table>

U.S. Pat. No. 6,083,532 discloses a sustained release tablet comprising a drug to be released at a controlled rate and a sustained release formulation comprising at least three different types of polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer wherein pH dependent gelling polymer comprises at least one of an alginate, a carboxyvinyl polymer, or a salt of a carboxymethyl cellulose; pH independent gelling polymer comprises at least one of a hydroxy propyl methyl cellulose, a hydroxy propyl ethyl cellulose, a hydroxy propyl cellulose, a hydroxy ethyl cellulose, a methyl cellulose, a
in gum or a polyethylene oxide; and enteric polymer comprises at least one of a polycrylate material, a cellulose acetate phthalate, a cellulose phthalate hydroxy propyl methyl ether, a polyvinyl acetate phthalate, a hydroxy propyl methyl cellulose acetate succinate, a cellulose acetate trimellitate, or a shellac.

U.S. Pat. No. 4,919,938 discloses a sustained release pharmaceutical composition in tablet form consisting essentially of a core matrix containing 20% to 60% by weight of a hydroxypropylmethylcellulose gelling agent, 0.41% to 20% by weight of (1)-trans-1a,2,3, 4a,5,6-hexahydro-9-hydroxy-4-(1-propyl)-4H-naphth [1,2-b]-1,4-oxazine hydrochloride, 2.08 to 12.5% by weight of buffering agent and suitable pharmaceutically acceptable excipients. A coating of a slowly soluble water permeable ethylcellulose polymer surrounds the core matrix.

U.S. Pat. No. 4,983,398 discloses a therapeutically active composition comprising a mixture of a therapeutically active medicament and a carrier base material, wherein the carrier base material consists essentially of one or more water-soluble, non-ionic cellulose ethers, wherein at least one of the cellulose ethers is a hydroxypropyl methylcellulose having a number average molecular weight of at least 50,000, and an alkali metal carboxylate. The carrier base comprises less than 30% by weight of the total weight of the composition.

U.S. Pat. No. 4,369,172 discloses a carrier base material combined with a therapeutically active medicament shaped and compressed to a solid unit dosage form having a regular and prolonged release pattern upon administration. The carrier base material is hydroxypropyl methylcellulose, or a mixture of hydroxypropyl methylcellulose and up to 30% by weight of a mixture of ethylcellulose and/or up to 30% by weight of the mixture of sodium carboxymethylcellulose, and wherein the hydroxypropyl methylcellulose has a hydroxypropyl content of 9-12% weight and a number average molecular weight of less than 50,000.
Pat. No. 4,557,925 discloses a controlled release pharmaceutical tablet comprising a drug and a coating applied thereon. The coating comprises a film-forming forming polymer which is insoluble in water and gastrointestinal fluids and consists essentially of a terpolymer of polyvinylchloride, polyvinyl acetate and polyvinyl alcohol, and a water soluble pore creating material randomly distributed in the terpolymer coating. The pore creating substance is present in an amount of one part to 35 parts for each one to ten parts of terpolymer.

U.S. Pat. No. 4,726,951 discloses a pharmaceutical composition for oral administration with selectively adjustable programmed release and controlled absorption, comprising miniaturized granules obtained by high to very high compression. The pharmaceutical composition comprises miniaturized granules (a) containing pH control agents, (b) coated with excipients determining the slow penetration of digestive liquids, and/or (c) coated with a very thin layer of liquids or mixture of such granules, with the relative proportion of (a), (b) and (c) adjusted to give the desired release of the active ingredient. Cephalexin is one of the active ingredients disclosed.

U.S. Pat. No. 5,051,262 discloses a delayed action programmed release pharmaceutical preparation of one or more medicament units suitable for oral administration, each unit comprising an inert core surrounded by at least one inner layer and one or more inert outer coatings. At least one of the inner layers comprises an active medicament, which has a solubility which varies with pH and is either basic or acidic, and at least one pH adjuster. The pH adjuster is an organic acid or organic acid salt if the medicament is basic, or an inorganic base or basic salt if the medicament is acidic. The pH adjuster is present in an amount sufficient to ensure that the rate of dissolution of the medicament is substantially independent of the pH of the environment in which dissolution occurs. Cephalexin is described as one of the possible medicaments.
Application WO 99/49868 discloses a sustained release cefaclor composition comprising 30 to 90 wt % of cefaclor, 5 to 60 wt % of a hydroswelling polymer and 1 to 10 wt % of a salt capable of releasing gaseous CO₂ in a gastric environment useful for administration once a day as well as twice a day. The amount of the salt added is critical as use of excessive amount of salt would generate excessive amount of CO₂ gas thereby irritating the stomach, disintegrating the formulation and losing the sustained release characteristic.

Japanese Patent JP 57165392A discloses a long-acting cephalaxin tablet comprising cephalaxin mixed with ≥10% w/w oils and fats (e.g. higher fatty acid, higher alcohol, alcohol ester, etc.) and with a vehicle such as microcrystalline cellulose and a lubricant such as magnesium stearate, and the mixture is pressed, formed to granules passing through a 20 mesh sieve, and subjected to the slug-forming process to obtain a high-quality long-acting tablet. The rate of dissolution of cephalaxin can be controlled by selecting the kind of oils and fats and the number of the times of slug formation process.


Patent application WO 98/22091 discloses a controlled release β-lactam antibiotic agent preferably amoxicillin trihydrate in a hydrophilic and/or hydrophobic polymeric matrix such that 50 % of the active is released within 3 to 4 hr from oral administration and remainder is released at a controlled rate. Examples include matrix tablets containing amoxicillin with hydroxypropyl methylcelluloses, amoxicillin with eudragit and alginate.

United States Patent 3,996,355 teaches permanent suspension dosage forms of water-sensitive drugs for administration without reconstitution. Amoxicillin-probenecid suspension dispersed in sesame oil containing sucrose as suspending agent and silica as thickening agent is exemplified.
 Patent No. RO 80932 discloses oral suspension of benzathine penicillin, procaine penicillin and probenecid with other excipients.

Japanese Patent JP 52105220A discloses suppository formulations of β-lactams. For example, a suppository capsule containing cephalexin, probenecid, peanut oil and polyoxyethylene cetyl ether.

Japanese Patent JP 52064418A discloses highly absorbable penicillin suppository formulation containing (4-ethyl-2,3-dioxo-1-piperazinyl carbonyl amino)-benzyl penicillin or its salt, probenecid, and peanut oil.

2.4 Drug substance

In this study, once a day formulation was to be developed for cefaclor in order to improve patient compliance and bring about life-cycle extension of the molecule.

Cefaclor is a semi synthetic, cephalosporin antibiotic for oral administration. Dosage forms of Cefaclor available in the market include capsules, dispersible tablets, extended release tablets, powder for oral suspension and redmix. Monographs of capsule, powder for oral suspension and extended release tablets are available in United States Pharmacopoeia and British Pharmacopoeia. Capsules are available in two strengths (250 & 500mg), dispersible tablets in two strengths (125 & 250mg), powder for oral suspension in three strengths (125,187 & 250mg/5ml), redmix in two strengths (125 7250mg/5ml) and extended release tablets in two strengths (375 & 500mg) for BID administration.
Physicochemical properties of drug substance

Cefaclor is an orally active cephalosporin, which due to its greater activity against Gram-negative bacteria, particularly *Haemophilus influenzae*, is often classified as a second-generation agent. Cefaclor is a white to cream colored crystalline powder. The material is odorless going to slightly sulphurous. Chemically it is 3-chloro-7-d-(2-phenylglycinamide)-3-cephem-4-carboxylic acid, monohydrate. Its molecular weight is 385.82.

![Chemical Structure of Cefaclor]

Polymorphs of cefaclor are possible. Such polymorphs are a function of the solvent from which cefaclor is crystallized. The only polymorph of general importance is cefaclor monohydrate. The X-ray powder diffraction data, as reported, for Cefaclor monohydrate is appended as Annexure 1.

The infrared spectrum of cefaclor monohydrate in potassium bromide pellet, as reported, is appended as Annexure 2.

The thermogram of cefaclor generally shows a small broad endotherm between 40°C and 120°C corresponding to the loss of water and other volatiles from the sample. The major endotherm in the DTA curve for cefaclor is observed around 220°C where the material decomposes. Cefaclor gives a reasonable thermo gravimetric curve and shows a loss of water and other volatiles from about 40°C to 120°C. At about 180°C, Cefaclor samples begin to lose weight indicating the beginning of decomposition of the sample.
Cefaclor is a reasonably stable molecule in the dry state. When cefaclor is present in the monohydrate crystalline form in the dry powder, two-year stability can be easily obtained. The powder becomes lightly yellow upon aging, however, little decrease in the potency of cefaclor is observed.

On degradation, cefaclor appears to lose HCl quite easily. Further degradation steps seem to be quite rapid and no other compounds have been isolated. In an attempt to generate such compounds, some studies have been carried out on the p-nitrobenzylester of cefaclor. This study showed that Cefaclor can undergo intramolecular nucleophilic attack by the side chain amine group to produce a diketopiperazine with the following structure:

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}}
\]

Cefaclor is stable in solutions of pH not higher than 4.5. Solutions prepared in pH2.5 and 4.5 buffers contain at least 90% of their initial activity after 72 hours at 4°C. In neutral or alkaline solutions, cefaclor undergoes a rapid loss of activity.
The pharmacopoeial specification of Cefaclor is summarized in table 2.8:

Table 2.8: Pharmacopoeial specifications of Cefaclor

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Compendial limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USP 25</td>
</tr>
<tr>
<td></td>
<td>BP 2002</td>
</tr>
<tr>
<td>Description</td>
<td>White to off white, crystalline powder. Slightly soluble in water, practically insoluble in methanol, in chloroform and in benzene.</td>
</tr>
<tr>
<td></td>
<td>A white or slightly yellow powder, slightly soluble in water, practically insoluble in methanol and in methylene chloride.</td>
</tr>
<tr>
<td>Identification</td>
<td>a) IR similar to USP Cefaclor RS</td>
</tr>
<tr>
<td></td>
<td>b) The retention time of assay preparation of test preparation corresponds to that of USP Cefaclor RS</td>
</tr>
<tr>
<td></td>
<td>a) IR: Similar to cefaclor CRS</td>
</tr>
<tr>
<td></td>
<td>b) By TLC: Similar to BP Cefaclor CRS</td>
</tr>
<tr>
<td></td>
<td>c) Color development</td>
</tr>
<tr>
<td>Crystallinity</td>
<td>Meets the requirements</td>
</tr>
<tr>
<td>pH</td>
<td>Between 3.0-4.5, in an aqueous suspension containing 25mg/mL</td>
</tr>
<tr>
<td></td>
<td>Between 3.0-4.5, in an aqueous suspension containing 25mg/mL</td>
</tr>
<tr>
<td>Water (by KF)</td>
<td>Between 3.0-6.5 %</td>
</tr>
<tr>
<td></td>
<td>Between 3.0-6.5 %</td>
</tr>
<tr>
<td>Specific optical rotation</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>+101° to +111°</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>30ppm</td>
</tr>
<tr>
<td>Chromatographic purity</td>
<td>NMT 0.5%</td>
</tr>
<tr>
<td>Individual related</td>
<td>NMT 0.5%</td>
</tr>
<tr>
<td>substance</td>
<td></td>
</tr>
<tr>
<td>Total related substances</td>
<td>NMT 2.0%</td>
</tr>
<tr>
<td></td>
<td>NMT 2.0%</td>
</tr>
<tr>
<td>Assay (HPLC)</td>
<td>950 to 1020µg of C_{15}H_{14}ClN_{3}O_{4}S per mg on anhydrous basis.</td>
</tr>
<tr>
<td></td>
<td>NLT 96.0 and NMT the equivalent of 102.0% of C_{15}H_{14}ClN_{3}O_{4}S on anhydrous basis.</td>
</tr>
</tbody>
</table>
Cefaclor is the second generation Cephalosporin that is active by oral route having antibacterial activity.

2.4.2.1 Sensitive Organisms

Cefaclor is more active than Cephalexin against Gram-positive bacteria, such as staphylococci and streptococci, but against Staph. aureus it is not as active as cephalothin. The drug is somewhat less resistant to staphylococcal beta-lactamase than Cephalexin and so it may not be a reliable anti-staphylococcal agent.\textsuperscript{32,33} Enterococcus faecalis is resistant\textsuperscript{34}. Cefaclor is more active than Cephalexin against many Gram-negative bacteria such as meningococci, gonococci, E.coli, Klebsiella pneumoniae, Pr. mirabilis and Salmonella and Shigellae spp.\textsuperscript{35,36,37} The drug is active against beta-lactamase-producing gonococci\textsuperscript{38}. Ampicillin-sensitive strains of H influenzae and most which are ampicillin – resistant because of beta-lactamase production are sensitive to Cefaclor. Most strains, which show intrinsic resistance to ampicillin, are Cefaclor resistant\textsuperscript{39}. Moraxella catarrhalis is also usually Cefaclor-sensitive. Cefaclor is inactive against Serratia, Providencia and Acinetobacter spp. and Pseudomonas aeruginosa. Most strains, of Pr. Vulgaris and Morganella morganii are also resistant\textsuperscript{40}. Anaerobic Gram-positive cocci and most Gram-negative anaerobes, other than those of Bacteroides fragilis group are usually cefaclor-sensitive. The Clostridium spp. are usually resistant\textsuperscript{41}.

The MICs of Cefaclor against some bacterial species are shown in table 2.9 \textsuperscript{42-45}.
Table 2.9: MICs of Cefaclor

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus (non-penicillinase producer)</em></td>
<td>2.0</td>
</tr>
<tr>
<td><em>Staphylococcus aureus (penicillinase producer)</em></td>
<td>2.0</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes (group A)</em></td>
<td>0.25</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>64.0</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>8.0</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>&gt;128.0</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>8.0</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>&gt;128.0</td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
<td>&gt;128.0</td>
</tr>
<tr>
<td><em>Providencia spp.</em></td>
<td>&gt;128.0</td>
</tr>
<tr>
<td><em>Serratia spp.</em></td>
<td>&gt;128.0</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2.0</td>
</tr>
</tbody>
</table>

2.4.2.2 Mechanism of Action

Cefaclor inhibits bacterial septum and cell wall synthesis, probably by acylation of membrane bound transpeptidase enzymes. This prevents cross-linkage of peptidoglycan chains, which is necessary for bacterial cell wall strength and rigidity.

2.4.2.3 Mode of Administration and Dosage

Oral doses of 250-500 mg, 6 hourly, are suitable for adults46. An adult dosage of 0.5 g, 8-hourly is also satisfactory47. In children, the dosage is 40-50 mg per kg body weight per day, given in three or four divided doses48. For the treatment of milder infections in children, a dosage of 40 mg per kg, given in two divided doses, is also satisfactory49.
Similar to amoxycillin and other drugs, Cefaclor in a dose of 2 g, can be used for single-dose treatment of acute uncomplicated urinary tract infections in adults\textsuperscript{50}.

Cefaclor’s half-life in normal subjects of 40-60 min, only increases to 3 h in anephric patients\textsuperscript{51}.

As a result, its dose can be reduced in patients with renal failure to a lesser extent than cephalexin. Patients with severe renal failure should receive 25\% of the usual dose, and those with moderate renal failure 50\% of the usual dose. In patients with mild renal failure (creatinine clearance >40 mL per min), modification of Cefaclor dosage is unnecessary\textsuperscript{52}.

2.4.2.4 Serum Levels in Relation to Dosage

The drug is rapidly absorbed from the gastrointestinal tract, but its peak and subsequent serum levels are lower than with cephalexin. After a 200-mg oral dose, the mean peak serum level at 1 h is 6 \( \mu g \) per ml (comparable level for cephalexin 9.4), which falls to 0.3\( \mu g \) per mL (cephalexin 0.68) at 4 h. Cefaclor is more rapidly excreted than cephalexin, their half-lives being 0.58 and 0.8 h, respectively\textsuperscript{46}. Concomitant administration of Probenecid prolongs the serum levels of Cefaclor. Food intake reduces the maximum concentration of the Cefaclor in the serum and prolongs the time to attain this concentration. However, the area-under-the concentration-time curve and urinary recovery of the drug are unaffected\textsuperscript{53}. The serum half-life of Cefaclor in patients with severe renal failure is only about 3 h, which suggests that it is also eliminated by non-renal mechanisms\textsuperscript{54}.

2.4.2.5 Toxicity

Therapy with this drug has been associated with a low frequency of side-effects. Gastrointestinal symptoms, such as diarrhea and nausea, have occurred in some 2.6\% of treated patients. Cefaclor only has a minor effect on the anaerobic intestinal microflora.

Hypersensitivity phenomena, such as allergic rashes, have been noted in 1.55\% of patients. Eosinophilia, positive Coombs’ test without hemolysis, reversible leukopenia and elevated SGOT levels have also been noted occasionally. Serum sickness-like reactions appear to occur more commonly with Cefaclor than with cephalexin. These reactions occur with Cefaclor because of the drug’ biotransformation in liver into immuogenic metabolites. An elevated
Urea occurs occasionally during Cefaclor therapy, but serious nephrotoxicity has not been observed. Animal experiments show that unilateral obstruction of the ureter increases the nephrotoxicity of Cefaclor and of other Cephalosporins, which are rapidly secreted across renal tubular cells.

2.4.2.6 Clinical Uses of Cefaclor

This drug has been satisfactory for the treatment of urinary tract infections, including cases of complicated and/or recurrent infections. Pyelonephritis caused by ampicillin-resistant organisms, such as Klebsiella spp., also responds to Cefaclor. Uncomplicated urinary tract infections in non-pregnant women may respond to 2g single-dose Cefaclor therapy. A single daily dose of 250 mg cefaclor is satisfactory as prophylactic antibiotic for patients with recurrent urinary infections. Cefaclor has been curative for children and adults with acute streptococcal pharyngitis, otitis media and maxillary sinusitis. In children with acute otitis media it is about as good as amoxicillin. It is effective in otitis media and sinusitis caused by β-lactamase-producing strains of *H.influenzae* and *Moraxella catarrhalis*. Cefaclor is ineffective for eradicating *H.influenzae* from pharyngeal carriers. It is about equally as effective as amoxicillin for the treatment of infective exacerbations of chronic bronchitis.

2.5 Polymers for preparing hydrophilic matrix

Xanthan gum and sodium alginate selected in the current study are high molecular weight biosynthetic polysaccharides and are extraordinarily enzymatically resistant. They offer potential utility as drug carriers because of their inertness and biocompatibility. A number of controlled drug release alginate systems have been studies such as gentamicin implants, pilocarpine ophthalmic film and sulfadiazine tablets.

2.5.1 Sodium Alginate

Alginic acid is a high molecular weight polysaccharide extracted from kelp(brown seaweed)and is neutralized with sodium carbonate to yield sodium alginate. Alginic acid is a linear copolymer of 1,4 linked β-D-mannuronic acid and α-L guluronic acid. The polymer chain consists essentially of three distinct polymer segments:

- Polymannuronic acid segments (M Blocks)
P-glucuronic acid segments (G blocks)
and segments of alternating or randomly distributed mannuronic acid and guluronic acid units
(G blocks)

The proportion of the 3 polymer segments varies between each species of kelp and imparts
distinctly different properties to the final product. By altering the guluronicate/manuronate
ratio of the alginate, one can alter the gelling properties of the drug matrix and subsequent
porosity of the gel. In turn, this will affect the rate of diffusion of the dissolved drug
throughout the matrix. M-rich alginates are the most effective in sustaining the release of the
drug from alginate powder tablets at acidic conditions. These are the most easily hydrating
alginites at low pH and therefore, upon hydration, build up the diffusion and erosion barrier
for the drug first. Recommended high M FMC products are Prontanal LF 240D and Protanal
LF10/60D (60-70%M). Protanal LF 240D has a viscosity of 70-150mPa.s and particle size of
240-mesh. Keltone HVCR of ISP Alginates, has a medium M/G range, particle size of 80-
mesh and viscosity of 400 mPa.s for a 1% dispersion.

Standards have been set forth for Sodium Alginate in the United States
Pharmacopeia/National Formulary, the European Pharmacopoeia, British Pharmacopoeia, the
Japanese Excipients Book and Food Chemicals Codex. Sodium alginate is considered
Generally Recognized as Safe (GRAS) by qualified experts and is in accordance with United
States Food and Drug Regulations.

Sodium alginate can be processed by direct compression, non aqueous granulation and
aqueous granulation processes.

Sodium alginate, being the water-soluble salt of alginic acid, is insoluble below pH 3.0 and
soluble above pH 3.0. This pH-dependent behavior of alginate can be exploited to customize
release profiles. The matrix formed by sodium alginate releases the drug slowly below pH 3.0
and shows faster release rate above pH 3.0. When ingested, the gastric fluid promotes a
polymer chain relaxation forming a swollen gel layer of nearly infinite viscosity around the
tablet. The hydrated sodium alginate is converted into a porous, insoluble alginic acid skin.
Once passed into the higher pH of the intestinal tract, the alginic acid skin is converted to a soluble viscous layer. This polymer matrix later begins eroding from the tablet surface into the gastro-intestinal fluid. Drug dissolution is dependent on both diffusion and erosion of tablet. Relative proportions of the released drug are determined by drug characteristics and the physiochemical nature of the gel layer.

Alginate salts can be used alone or in combination with other polymers such as xanthan gum to control drug release from hydrophilic matrix tablet.

One of the most important and useful properties of alginates is the ability to form gels by reaction with calcium salts\(^{61,62}\). These gels, which resemble a solid in retaining their shape and resisting stress, consist of almost 100% water. The cross links are proposed to have been caused either by simple ionic bridging of two carboxyl groups on the adjacent polymer chains via calcium ions or by chelation of single calcium ions by hydroxyl and carboxyl groups on each of a pair of polymer chains. Although these bonds may play a role in the gelation mechanism, they are not sufficiently energetically favorable to account for the gelation of alginate. It has been shown on the basis of fiber diffraction data and model building calculations that the shape of both polymannuronic acid segments and the polyguluronic acid segments of alginic acid is ribbon-like and extended and that these extended ribbons can stack together in sheets. On the basis of these data and the properties of gels, it has been suggested that the cooperative association of either polymannuronic acid segments or polyguluronic acid segments is involved in the formation of the cross linked network of polymer chains.

2.5.2 Xanthan gum

Xanthan gum is a high molecular weight natural carbohydrate produced in a pure culture fermentation process by the Xanthomonas campestris microorganism. In the fermentation process, Xanthomonas campestris is cultured in a well-aerated medium containing glucose, a suitable nitrogen source, di-potassium hydrogen phosphate and trace elements. To provide seed for the final fermentation, the microorganism is grown in several stages with associated
identication tests prior to introduction into the final fermentation medium. At the conclusion of the fermentation process, xanthan gum is recovered by precipitation in isopropyl alcohol and then dried and milled. Xanthan gum is less prone to natural variation unlike naturally occurring gums. It is of unvarying chemical structure and has uniform chemical and physical properties.

Each xanthan gum repeat unit contains five sugar residues: two glucose; two mannose, and one glucuronic acid. The polymer backbone consists of four β-D-glucose units linked at the 1 and 4 positions and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydro-glucose units distinguish xanthan from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the mannose nearest the main chain carries a single group at C-6. The resulting stiff polymer chain may exist in solution, as a single, double or triple helix which interacts with other xanthan gum molecules to form complex, loosely bound networks.63,64

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers and preservatives since precipitation occurs. Under highly alkaline conditions polyvalent metal ions, such as calcium, cause gelation or precipitation. Xanthan gum solutions are stable in the presence of up to 60% water miscible organic solvents such as acetone, methanol, ethanol or propanol. However, above this concentration precipitation or gelation occurs.65

When formulation comprising a sustained release carrier comprising a major proportion of xanthan gum, and the pharmacologically active ingredient comes into contact with an aqueous medium, the xanthan gum in the portion of the formulation exposed to the aqueous medium hydrates and swells to form a gel. Xanthan gum has a good swelling action on contact with an aqueous medium and overcomes the problems encountered by gums which either do not hydrate rapidly enough or hydrate too rapidly. Gums which do not readily hydrate are generally unable to hold the tablet together as, on exposure to an aqueous medium, the tablet

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break up before the gel fully hydrates. Gums which hydrate too rapidly generally also break up quickly as the gel formed is usually very weak and is unable to hold the tablet together. The thickness of the gel surrounding the central core of composition is intermediate between that of the thin layer when a hard gel is formed, as formed by Hydroxypropyl Methylcellulose gels for example and the thick layer when a soft gel is formed. In addition the nature of the gel formed is such that unlike hard gels it may be readily deformed, unlike soft gels it is not disrupted by such deformation and in-vivo it may be expected to pass obstructions and not be impeded in the gastro-intestinal tract.

Gelling of xanthan gum is temperature independent, pH independent and allows the active ingredient to diffuse out of the formulation at a steady rate as the medicament passes through the digestive system irrespective of the pH. Thus any formulation containing it, is adapted to provide sustained release both in the acidic media of the stomach and also in the intestines.

The use of xanthan gum in the sustained release carrier generally allows a slower release of active ingredient into the body as compared to the use of naturally occurring hydrophilic gums. As a result, this provides the advantage that the proportion of sustained release carrier in the formulation may be reduced compared to most other sustained release formulations, thus enabling the sustained release formulation to be provided in a relatively small solid dosage form if desired66.

2.5.3 Hydroxypropyl Methylcellulose Phthalate

It is prepared by the esterification of hydroxypropyl methylcellulose with phthalic anhydride. Several different types of HPMC are commercially available with molecular weights in the range of 20000-200000. It is used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug release properties; the release rate is pH dependent. When so used, it is dissolved in either dichlormethane:ethanol or ethanol:water solvent mixture67,68.
2.1 Reference Listed Drug

A BID formulation of cefaclor is marketed by Eli Lilly under the brand name of CECLOR CD in USA. It is available in 2 strengths: 375mg and 500mg. The details of this product as described in Physician’s Desk Reference are as follows:

2.6.1.1 Composition

Each Cefaclor CD tablet contains Cefaclor monohydrate equivalent to 375 mg (1.02 mmol) or 500 mg (1.36 mmol) anhydrous Cefaclor.

In addition, each extended release tablet contains the following inactive ingredients: cellulose; FD&C Blue No.2; magnesium stearate; mannitol; methacrylic acid copolymer type C; propylene glycol; Stearic acid; titanium dioxide; polyethylene glycol; talc; and edible black ink.

2.6.1.2 Pharmacokinetics: The Cefaclor CD formulation of Cefaclor is pharmacokinetically different from Ceflorn Pulvules® (conventional tablets of Cefaclor) formulation as can be seen from Table 2.10:

Table 2.10: Comparative pharmacokinetics of cefaclor pulvules Vs cefaclor CD in fasting and fed states

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cefaclor CD</th>
<th>Cefaclor CD</th>
<th>Cefaclor Pulvules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>375 mg</td>
<td>500 mg</td>
<td></td>
</tr>
<tr>
<td>n=10</td>
<td>n=16</td>
<td>n=16</td>
<td></td>
</tr>
<tr>
<td>fed</td>
<td>fasted</td>
<td>fed</td>
<td>fasted</td>
</tr>
<tr>
<td>Cmax</td>
<td>3.7 (1.1)</td>
<td>NA</td>
<td>8.2 (4.2)</td>
</tr>
<tr>
<td>T_max</td>
<td>2.7 (1.0)</td>
<td>NA</td>
<td>2.5 (0.8)</td>
</tr>
<tr>
<td>AUC</td>
<td>9.9 (2.2)</td>
<td>NA</td>
<td>18.1 (4.2)</td>
</tr>
<tr>
<td></td>
<td>2 x 250 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=15</td>
<td>n =16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fed</td>
<td>fasted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td>9.3 (2.7)</td>
<td>16.8 (4.7)</td>
<td></td>
</tr>
<tr>
<td>T_max</td>
<td>1.5 (0.6)</td>
<td>0.9 (0.4)</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>20.5 (2.8)</td>
<td>19.2 (5.0)</td>
<td></td>
</tr>
</tbody>
</table>

(± 1 standard deviation)

NA = data not available

No direct comparisons with the suspension formulation of Cefaclor have been conducted; therefore, there are no data with which to compare the suspension formulation. Until further data are available, the pharmacokinetic equivalence of the CD and the suspension formulations should NOT be assumed.
Absorption and Metabolism: The extent of absorption (AUC) and the maximum plasma concentration (C_max) of Cefaclor from Cefclor CD are greater when the extended release tablet is taken with food. No drug accumulation was noted when Cefclor CD was given twice daily. The plasma half-life in healthy subjects is independent of dosage form and averages approximately 1 hour.

Food Effect on Pharmacokinetics: When Cefclor CD is taken with food, the AUC is 10% lower while the Cmax is 12% lower and occurs 1 hour later compared to Cefclor Pulvules. In contrast, when Cefclor CD is taken without food, the AUC is 23% lower while the Cmax is 67% lower and occurs 0.6 hours later using an equivalent milligram dose of Cefclor Pulvules as a reference. Therefore, Cefclor CD should be taken with food.

2.6.1.3 Indications and usage

When administered at the recommended dosages and durations of therapy, Cefclor CD is indicated for the treatment of patients with the following mild to moderate infections when caused by susceptible strains of the designated organisms.

-acute bacterial exacerbations of chronic bronchitis due to Haemophilus influenzae (non-β-lactamases-producing strains only), Moraxella carrrhalis (including β-lactamases-producing strains) or Streptococcus pneumoniae. (In view of the insufficient numbers of isolates of β-lactamases-producing strains of Haemophilus influenza that were obtained from clinical trials with Cefclor CD for patients with acute bacterial exacerbations of chronic bronchitis or secondary bacterial infections of acute bronchitis, it was not possible to adequately evaluate the effectiveness of Cefclor CD for bronchitis known, suspected or considered potentially to be caused by β-lactamase-producing H-influenzae.)

- secondary bacterial infections of acute bronchitis due to Haemophilus influenzae (non-β-lactamase-producing strains), or Streptococcus pneumoniae.

- pharyngitis and tonsillitis due to Streptococcus pyogenes.

- uncomplicated skin and skin and structure infections due to Staphylococcus pyogenes that were obtained from clinical trials with Cefclor CD for patients with uncomplicated skin and skin structure infections, it was not possible to adequately evaluate effectiveness of Cefclor CD for skin infections known, suspected, or considered potentially to be caused by S.pyogenes.
Contraindications
Cefaclor CD is contraindicated in patients with known hypersensitivity to Cefaclor and other Cephalosporins.

2.6.1.5 Precautions
General: Superinfection (overgrowth by non susceptible organisms) should always be considered a possibility in a patient being treated with a broad-spectrum antimicrobial. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Drug Interactions:
Antacids- the extent of absorption of Cefaclor CD is diminished if magnesium or aluminum hydroxide-containing ant-acids are taken within 1 hour of administration; H2 blockers do not alter either the rate or the extend of absorption of Cefaclor CD.

Probenecid- The renal excretion of Cefaclor is inhibited by Probenecid.

Warfarin- there have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Cefaclor and warfarin concomitantly. No specific studies have been performed to rule in or rule out this potential drug/drug interaction.

Laboratory Test Interactions: Administration of Cefaclor CD may result in a false-positive reaction for glucose in the urine. This phenomenon has been seen in patients taking Cephalosporin antibiotics when the test is performed using Benedict’s and Fehling’s solutions and also with Clinitest® tablets.

Labor and Delivery: Cefaclor CD has not been studied for use during labor and delivery. Treatment should be given only if clearly needed.

Nursing Mothers: No studies in lactating women have been performed with Cefaclor CD. Small amounts of Cefaclor (≤ 0.21 µg/mL) have been detected in human milk following administration of single 500-mg doses of Cefaclor. The effect on nursing infants is not known. Caution should be exercised when Cefaclor CD is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Cefaclor CD in pediatric patients less than 16 years of age have not been established.
2.6.1.5 Adverse reactions

Clinical Trials: There were 3272 patients treated with multiple doses of Cefaclor CD in controlled clinical trials and an additional 211 subjects in pharmacology studies. There were no deaths in these trials thought to be related to toxicity from Cefaclor CD. Treatment was discontinued in 1.7% of patients due to adverse events thought to be possibly or probably drug-related.

The following adverse clinical and laboratory events were reported during the Cefaclor CD clinical trials conducted in North America at doses of 375 mg or 500 mg BID; however, relatedness of the adverse events to the drug was not assigned by clinical investigations during the trials. Adverse reactions occurring during the clinical trials with Cefaclor extended release tablets with an incidence of less than 1% but greater than 0.1% included the following (listed alphabetically):

Accidental injury, anorexia, anxiety, arthralgia, asthma, bronchitis, chest pain, chills, congestive heart failure, conjunctivitis, constipation, dizziness, dysmenorrhea, dyspepsia, dysuria, ear pain, edema, fever, flatulence, flu syndrome, gastritis, infection insomnia, leucorrhoea, lung disorder, maculopapular rash, malaise, menstrual disorder, myalgia, nausea and vomiting, neck pain, nervousness, nocturia, oitis media, pain, palpitation, peripheral edema, rash, respiratory disorder, sinusitis, somnolence, sweating, tremor urticaria, vomiting.

One case of serum-sickness-like reaction was reported among the 3272 adult patients treated with Cefaclor have also been reported with the use of Cefaclor in other oral formulation and are
these are frequently in pediatric patients than in adults. These reactions are characterized by findings of erythema multiforme, rash, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes and no evidence to date of sequelae of the reaction. Such reactions have been reported with overall occurrence ranging from 1 in 200 (0.5%) in one focused trial; to 2 in 8346 (0.024%) in overall clinical trials (with an incidence in pediatric patients in all clinical trials of 0.055%); to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. Occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = 2 to 3 days, based on postmarketing surveillance studies). In those patients requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in pediatric patients.

In Postmarketing Experience: In addition to the events reported during clinical trials with Cefalor CD, the following adverse experiences are among those that have been reported during worldwide postmarketing surveillance: allergic reaction, anaphylactoid reaction, angioedema, face edema, hypotension, Stevens-Johnson syndrome, syncope, paresthesia, vasodilatation, and vertigo.

Clinical: Severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis, have been reported rarely. Anaphylactoid events may be manifested by solitary symptoms, including angioedema, edema (including face and limbs), parasthesias, syncope, or vasodilatation. Anaphylaxis may be more common in patients with a history of penicillin allergy. Rarely, hypersensitivity symptoms may persist for several months.
Dosage and administration

The absorption of Cefaclor CD is enhanced when it is administered with food. Therefore, Cefaclor CD should be administered with meals (i.e., at least within one hour of eating). The extended release tablets should not be cut, crushed, or chewed. The dosage is as shown in the following Table 2.11:

Table 2.11: Dosage regimen of Cefaclor CD

<table>
<thead>
<tr>
<th>Adults (age 16 years and older)</th>
<th>Total Daily Dose</th>
<th>Dose and Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Bacterial Exacerbations of Chronic Bronchitis due to H.influenzae (non-β-lactamase-producing strains), or Streptococcus pneumoniae</td>
<td>1000 mg</td>
<td>500 mg q 12 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Secondary Bacterial Infections of Acute Bronchitis due to H.influenzae (non-β-lactamase-producing strains only), M.catarrhalis (including β-lactamase-producing strains), or S.pneumoniae</td>
<td>1000 mg</td>
<td>500 mg q 12 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Pharyngitis and / or tonsillitis due to S.pyogenes</td>
<td>750 mg</td>
<td>375 mg q 12 hours</td>
<td>10 days</td>
</tr>
<tr>
<td>Uncomplicated Skin and Skin Structure infections due to S.aureus (methicillin-susceptible strains)</td>
<td>750 mg</td>
<td>375 mg q 12 hours</td>
<td>7 – 10 days</td>
</tr>
</tbody>
</table>

500 mg BID of Cefaclor CD is clinically equivalent to 250 mg TID of Cefaclor as a pulvule in those indications listed in the section 2.4.1.3. 500 mg BID of Cefaclor CD is NOT equivalent to 500 mg TID of other Cefaclor formulations. Elderly patients with normal renal function do not require dosage adjustment.
2.1 Clinical studies

In adequate and well-controlled clinical trials of Ceclor CD in the treatment of acute bacterial exacerbations of chronic bronchitis (ABECB) and secondary bacterial infection of acute bronchitis (SBIAB), only 4 evaluable patients with SBIAB had infections caused by β-lactamase-producing H. influenzae. Four patients do not provide adequate data upon which to judge clinical efficacy of Ceclor CD against β-lactamase-producing H. influenzae.

(ii) Ceclor CD (375 mg Q12H) (n=115) was compared to Ceclor Pulvules (250 mg TID) (n =106) for the treatment of patients with uncomplicated skin and skin structure infections, including cellulites, pyoderma, abscess, and impetigo. Patients were treated for 7 to 10 days and were evaluated for clinical resolution and bacterial eradication approximately one week after completing therapy. To be evaluable, all patients had to have a recognized pathogen isolated from the skin infection just prior to the initiation of therapy. The results of this randomized, double-blinded, U.S. trial demonstrated:

a) overall clinical cure rates were 72% (83 of 115 patients) and 75% (80 of 106 patients), respectively for Ceclor CD and Ceclor Pulvules (95% CI around 3% difference=−16% to +9%),

b) overall bacteriologic eradication rates against Straphylococcus aureus were comparable

2.1.8 How supplied

Tablet (extended release):
375 mg, blue (UC 5391)–(60s)
500 mg, blue (UC 53492)-(60s)
500 mg, blue (UC5392) –(14s)

2.1.9 Storage condition

Store at controlled room temperature, 15° to 30°C (59° to 86°F).
2.6 Pharmacopoeial requirements for extended release tablets of Cefaclor

The compendial monograph for Cefaclor extended release tablets is available in USP and BP. The specifications for the drug product are shown in the following table 2.12:

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Compendial limits</th>
</tr>
</thead>
</table>
| Identification     | Retention time of major peak in chromatogram of assay preparation correspond to that in the chromatogram of standard preparation as obtained in assay. | a)UV  
b)Retention time of major peak in chromatogram of assay preparation correspond to that in the chromatogram of standard preparation as obtained in assay. |
| Dissolution        | Medium 0.1 N HCl, 900 mL  
Apparatus 1: 100 rpm  
The percentage of the label claim of Cefaclor dissolved at specified times conform the limit:  
| Time (Min) | Amount dissolved | A suitable dissolution test is carried out to demonstrate the appropriate release of Cefaclor. The dissolution profile reflects the \textit{in vivo} performance, which in turn is compatible with dosage schedule, recommended by manufacturer. |
| 30          | 5 - 30 %       |                               |
| 60          | 20 - 50 %      |                               |
| 240         | NLT 80.0 %     |                               |
| Uniformity of dosage units | Meets the requirement | - |
| Water          | NMT 7.0%       | - |
| Assay          | Cefaclor tablets contain the equi. of NLT 90.0% and NMT 110.0% of the labeled amount of \( \text{C}_{13}\text{H}_{14}\text{ClN}_{3}\text{O}_{4}\text{S} \) | 90.0-105.0% of the stated amount of anhydrous cefaclor |
| Packaging and storage | Preserve in tight, light resistant containers | Store at a temperature not exceeding 30°C |

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Conclusions from literature surveyed

Cefaclor exhibits pH dependent aqueous solubility.

- On account of sensitivity of cephalosporins to moisture and heat, a manufacturing process based on dry granulation or non aqueous wet granulation would improve stability of the drug product.
- Cefaclor has a short half life and hence to maintain the concentration above MIC, QID/BID dosing is required for immediate release products. Hence it is an ideal candidate for development of “dose dependent” to “rate controlled” extended release formulation in order to improve patient convenience and compliance.
- Although a number of patents exist for the BID formulation of cefaclor, none exist for OD formulation.
- The patents for preparing BID matrix formulations revealed the use of various cellulose polymers like Hydroxypropyl Methylcellulose, Ethyl cellulose, Hydroxypropyl cellulose, Hydroxyethyl cellulose, Methylcellulose besides Acrylic acid polymers, Xanthan gum, Sodium alginate, Cellulose acetate phthalate and Shellac.
- The major disadvantage of using the cellulose polymers is that they are required to be used in higher concentrations and with high dose high frequency drugs, the matrix formulation becomes too big for human consumption.
- Xanthan gum, has pH independent swelling characteristics and swells considerably at very low concentrations. Thus it is required to be added in relatively lower concentrations than most sustaining polymers and hence is suitable for extended release products of high dose high frequency drugs.
- Sodium alginate, shows a pH dependent release profile, with a slow release below pH 3.0 and faster one above pH3.0. This behavior can be exploited to customize release profiles.
- Sodium alginate gels can be stabilized by addition of Calcium ions.
- Alginate salts can be used alone or in combination with other polymers such as xanthan gum to control drug release from hydrophilic matrix tablet.
Cefaclor absorption is restricted to proximal part of gastrointestinal tract. Hence the polymer system used in the matrix should contain a mixture of pH-dependent and pH independent polymers so as to reduce the effect of pH on the release rate of the drug substance.

- Based on the dissolution method and profiles mentioned in various patents for the BID product, the following method and limits could be adopted during formulation development of this product:

  **Dissolution medium:**
  0.1N HCl: for the first hour
  pH 6.8 Phosphate buffer: from 1 hour to 4 hours

  **Apparatus:** USP Type 1, 100rpm

  **Limits:**

<table>
<thead>
<tr>
<th>Time</th>
<th>% released</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td>20-50%</td>
</tr>
<tr>
<td>2 hr</td>
<td>40-60%</td>
</tr>
<tr>
<td>3 hr</td>
<td>60-90%</td>
</tr>
<tr>
<td>4 hr</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

For the OD product, the following method could be adopted during formulation development:

  **Dissolution medium:**
  0.1N HCl: for the two hour
  pH 6.8 Phosphate buffer: after the second hour

  **Apparatus:** USP Type 1, 100rpm

  The dissolution profile for the OD product can be decided based on the BID product’s *in-vitro- in-vivo* correlation.

- For cefaclor, as for all β-lactum antibiotics, elevation of the drug concentration above a critical value, which tends to be the minimal inhibitory concentration (MIC), is not associated with increased bacteriocidal potency. High concentrations are associated with reduced potency.

- There is a direct correlation between the time above MIC (T>MIC) and antimicrobial potency with 90% bacteriological cure being effected if T>MIC is greater than 40%.
Cefaclor follows linear pharmacokinetics. Thus increasing the dose increases AUC linearly. In extended release systems, the rate of absorption is governed by release of drug from the dosage form, which can lead to reduction in AUC and hence efficacy. To avoid this, it is important to ensure that the AUC achieved by the extended release system is comparable to that achieved by an equal dose of immediate release dosage form.

- The excretion of cefaclor is reduced when given concurrently with probenecid resulting in increased and prolonged antibiotic serum concentration and prolonged half life. Hence co-administration of probenecid with a lower dose of cefaclor extended release formulation could prolong the T>MIC besides resulting in a comparable AUC.

- The absorption of Cefaclor is affected by food. Hence bioavailability/bioequivalence study must be performed in fed volunteers.

Based on the above literature findings, it was evident that there is a need for a simple, easy to make and cost effective cefaclor composition, which can be administered twice/once daily. The study objectives were redefined as follows:

i) To design a OCRS-BID of Cefaclor such that 90% confidence interval for the $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ is in line with USFDA/EMEA guidelines with respect to Cefaclor CD, 500mg.

ii) To design a OCRS-OD containing 1000/1500mg of Cefaclor, with or without Probenecid, such that the ratio of test to reference for $C_{\text{max}}$ and $AUC_{0-\infty}$ is in line with USFDA/EMEA guidelines with respect to 3 capsules of 500mg of the conventional product, the $T>MIC(1\mu g/mL)$ is greater than 40% of the dosing interval and $t_{1/2}$ is prolonged.