prepared with 100 mg of HPMC. After the in vitro release study, it was found that tablet A possessed slower erosion rate and tablet B possessed faster erosion rate. Both the tablet showed similar release rates under mild conditions. However, tablet B showed a faster release under highly destructive conditions that is for rotating-basket method at 150 rpm. In vivo release rates of the tablets were studied by administering the tablets to healthy volunteers under fasted and fed state. The in vivo release of B was found to be faster than A. This was attributed to the faster erosion of B as a result of destructive forces of the GIT. Hence, erosion rate affected the release rate of the tablets. Hence, during the development of a CR dosage form, the effects of the destructive forces of the GIT on tablet erosion and release inhibition in the colon must be carefully considered [81].

Study also revealed that matrix erosion is the rate-limiting step for release of water-insoluble drugs. Yin et al. used synchrotron radiation X-ray computed microtomography with a resolution of 9 μm to study the hydration and quantify the relative importance of erosion and swelling on the release of felodipine by statistical modeling. This tool proved to be efficient from a structural point of view in the quantification [79].

6.3. Pharmacokinetic Evaluation of Solid Oral-Controlled Dosage Forms

There is an increase in demand for controlled-released formulations as they provide various advantages over the conventional dosage forms. Preclinical pharmacokinetic studies can demonstrate the outcomes of the designed formulation in in-vivo animal models. Furthermore, these preclinical studies can be compared with the immediate-release formulations and other formulations of the same drug. Several preclinical studies on solid oral controlled-release dosage form were investigated and explored further for in vitro-in vivo correlation. Human clinical studies or bioavailability studies of controlled-release formulation provide actual insight and are required for regulatory submission ([57,58,82]).

Pharmacokinetic principles provide an evidence in the early stages of controlled-release formulations development if the drug is a suitable candidate for the given formulation, for the release rate of the system, and for the required dose for the specific therapeutic actions. Pharmacokinetic concepts can be used as a tool in the development of controlled-release dosage form, which can help in reducing the time and expense for the formulation development. A controlled-release dosage form was developed on the basis that there was a relationship between the pharmacological activity and the characteristics of systemic exposure to the drug [83, 84].

Pharmacokinetic evaluation studies are essential to characterize the controlled-release formulation in vivo. The evaluation studies are based on the concentration measurements of the APIs or their metabolites, in combination with determination of an acute pharmacodynamic effect. It is essential to measure the active metabolites as a change in absorption rate or in route of administration, and there may be modifications to the extent and the pattern of the metabolism [85, 86].

The pharmacokinetic studies are conducted by investigating the following:

1. The rate and extent of drug absorption.
2. Drug concentration fluctuations at steady state.
3. Intersubject variability arising because of drug formulation.
4. Proportionality of the dose.
5. Risk of dose dumping.
6. Factors affecting the performance of the controlled-release formulations [87].

These above-mentioned studies can be performed in healthy volunteers and in patients. When there is an administration of multiple doses, there is a need for providing evidence that steady state has been reached. The achievement of the steady state must be evaluated. This is done by collecting three predose concentrations for each formulation and comparing. When there is an evidence of no accumulation, there is no requirement of multiple dose studies [22].

6.3.1. Rate and extent of absorption and plasma drug fluctuations

This study can be assessed by comparing a controlled-release drug with an immediate-release drug after the administration of a single dose. For single-dose studies, the desired pharmacokinetic parameters of interests may include $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max}, t_{max}, $t_{1/2}$, and t_{lag} and for multiple dose studies, $AUC_{(0-\tau)}$, $t_{max,ss}$, $C_{max,ss}$, $C_{min,ss}$, and fluctuation.

It is necessary to provide an evidence that the controlled-release formulation has attained the required therapeutic concentration. Furthermore, the in vivo plasma drug profile can be correlated with the in vitro drug release profile. To obtain the cumulative absorption or in vivo release versus time profile for the controlled-release formulation, it is necessary to employ deconvolution of the concentration-time data. The calculated in vivo drug release or the fraction of in vivo drug release is correlated with in vitro drug release of the same batch of the product to establish IVIVC. The correlation can be utilized for getting biowaiver for regulatory approval [88] [87].