Breakthrough pain (BTP), a transient exacerbation of pain in patients with chronic pain receiving long-term opioid therapy, is a common and often unpredictable event. BTP episodes can vary among individuals, with onset of pain ranging from a few minutes to ≥30 minutes and duration of pain ranging from several minutes up to 2 hours. The onset of analgesia with traditional short-acting opioids (approximately 30-45 minutes) may be inadequate for many patients suffering from breakthrough pain. Recent advances in drug delivery technology have allowed for development of novel formulations of fentanyl that have pharmacokinetic profiles more consistent with the time course of BTP episodes and, as a result, these therapeutics may be more appropriate for the treatment of patients with BTP receiving long-term opioid therapy. Two formulations which have been developed for the treatment of BTP are FBT (fentanyl buccal tablet) and INFS (intranasal fentanyl spray). Both are approved for treatment in patients with cancer-related BTP who are receiving long-term opioid therapy. In separate studies, both formulations are highly bioavailable, reach maximum or near maximum concentration rapidly, and exhibit a decline from peak concentration that is characteristic of fentanyl. These shared pharmacokinetic characteristics result in a mean drug exposure profile that more closely corresponds to an average BTP episode. In clinical studies, these formulations have also shown onset of pain relief within 5-15 minutes and duration of relief up to 2 hours. There are pharmacokinetic features which differentiate the formulations from one another. Given the substantial variability of BTP experienced by each patient, these pharmacokinetic differences may provide useful information for physicians. No studies have been performed to directly compare the pharmacokinetics of these novel formulations of fentanyl. This review will describe the known pharmacokinetic profiles of FBT and INFS, from separate studies, to show the key differentiating characteristics of each medication.