Journal of Current Pharma Research
(An Official Publication of Human Journals)
An International Peer Reviewed Journal For Pharmacy, Medical & Biological Science
DOI: 10.25166 CODEN: JCPRD6 NLM ID: 101744065
ISSN: Print: 2230-7834 Online: 2230-7842
SJIF Impact Factor: 6.913

Human Journals
Review Article
November 2022 Vol.:16, Issue:2

Newer Drug Delivery Systems Shaping Clinical Preferences: Focus on Paracetamol, an Indian Perspective

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Submitted: 05 November 2022
Accepted: 22 November 2022
Published: 30 November 2022

Keywords: Paracetamol, Osteoarthritis, Oral dosage form, Crocin advance, Optizorb technology, India

ABSTRACT

Of various routes of administration of drugs like oral, intravenous (IV), intramuscular (IM), etc, the oral pathway remains the most suited for common use due to its unique advantages, including higher patient compliance, the possibility of leveraging delivery mechanisms- controllable and sustained drug delivery, ease of administration and feasibility for almost all solid formulations. Along with the advantages, the oral pathway has its limitations too- having variable absorption rates and variable serum concentrations leading to unpredictable effects, propensity for nausea and vomiting, acid labile actives, slower onset of action, etc. The efforts to overcome these limitations have driven various development in pharmaceutical science, helping create delivery mechanisms that offer distinct pharmacokinetic advantages/differentials to overcome challenges and offer patient benefits. Paracetamol as a drug is marketed for over 40 years in India and it remains the first-line drug for the management of fever, and is consistently recommended in most national and international guidelines as a first-line therapy option for common pain conditions like osteoarthritis, etc. Paracetamol is available in several oral formulations, but they have their drawbacks such as inter-patient variability, inconsistent therapeutic effects, and lack of quicker onset on the action. To cater to these unmet needs in India, Crocin (paracetamol) advanced with Optizorb technology with its consistent therapeutic effects and faster disintegration time leading to a proven quicker onset of action was developed for antipyretic action or acute/chronic pain relief.

INTRODUCTION:

Routes of drug administration and the corresponding physicochemical characteristics of a given route play significant roles in therapeutic efficacy and short-term/long-term biological effects. There are various routes for drug administration that cater to various clinical needs, the commonly used are oral, intravenous (IV), intramuscular (IM), and topical, each of them having its distinct advantages as well as limitations.[1] Other route, such as ocular delivery, have also been developed for localized, site-specific drug administration without unwanted systemic side effects.[1] Oral drug delivery (ODD) is the most preferred and convenient route of drug administration, due to its unique advantages, including patient compliance, controllable and sustained delivery, ease of administration and feasibility, cost-effectiveness, least sterility constraints, flexibility in the design of dosage form and ease of production.[1, 2] In addition, a large surface area lined with a viscous mucosal layer paves the way for drug attachment and subsequent absorption. However, in comparison with other routes, the absorption mechanism of oral drugs is more complex.[1]

Oral drugs usually consist of an active pharmaceutical ingredient (API) and excipients. After oral administration, absorption of the API from the solid dosage form depends on the permeability and solubility of the API, as well as on the release of the API from the dosage form which depends on the physicochemical features of the API, the composition of the excipient among other factors.[3]

Many APIs exhibit low dissolution rates, or/and poor solubility in aqueous environments such as the luminal fluids of the gastrointestinal tract resulting in poor oral bioavailability of these compounds. To improve the bioavailability of these poorly soluble drugs, formulation strategies have been derived that improve their dissolution rates as well as their aqueous solubility. Concerning formulation approaches, excipients are incorporated to assist in the dissolution process of the drug, or specialized dosage forms can be formulated that improve their dissolution rate through various mechanisms. Excipients can act as alkalinizing agents, surfactants, or filler material amongst other things.[4]

Orally administered drugs can be absorbed in either of the following pathways: para-cellular trans-cellular, carrier-mediated trans-cellular, and facilitated transport. Among these, the trans-cellular pathway is the most used mechanism. The challenges of drug absorption or efficacy do not only limit to solubility properties of the APIs or barriers met in the gut, but also the hepatic barriers after they enter intestinal epithelium. Another important factor to

consider is the low acidic pH of the gastric environment which degrades acid-labile drugs before they reach the large absorptive area of the intestine, preventing their disintegration in the neutral part of the small intestine, their primary absorption site, in their most concentrated form.[2]Some of the known challenges associated with the oral route of drug administration:[2, 5-12]

- Poor bioavailability and slow tablet disintegration
- Slower onset of action
- Variable absorption and varied serum concentrations- unpredictable therapeutic effects
- Irritation of gastric mucosa and associated nausea/vomiting
- Destruction or degradation of API by gastric acids
- Unpleasant taste or smell
- Inactivated the actives in the liver on their way to the systemic circulation

To overcome some of these challenges and cater to unmet needs, researchers have focused on the development of various novel oral drug delivery systems. These include formulations like the enteric coated, sustained release, immediate release, sugar-coated, intestinal patch systems, micro-needle capsules, and particulate. The micro-needle capsule pierces the mucosa directly with micro-needles and increases the penetration rate of drug molecules. Particulate devices are the most used oral vehicles, they are being investigated for the encapsulation and targeting of a vast variety of therapeutics. Some of these technologies are still in the preclinical stage. Therefore, continued research efforts are needed to solve these challenges and prove their feasibility in clinical use.[1]

Paracetamol

Paracetamol /acetaminophen was synthesized in 1878 by Morse and first used clinically by von Mering in 1887, Brodie and Axelrod led its “rediscovery” and in 1950, its marketing was started in the USA as an analgesic.[13, 14] Paracetamol/acetaminophen is one of the most commonly used antipyretic/analgesic drug used around the world, it has been available without a prescription for over 60 years[15]and is available as a conventional liquid, suppository, capsule, tablet/caplet, effervescent, mouth dissolving, injectable, and others like Panadol with Optizorb technology which is made available by GSK globally in over 100

countries, registered and available as Crocin in India. Paracetamol has a well-established benefit-risk profile and is consistently recommended in most national and international guidelines as first-line therapy as a prescription or non-prescription option (figure-1)[16]for common pain conditions such as dental pain, migraine, acute back pain, postoperative pain, etc.[15]It remains the drug of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAID), such as people with peptic ulcer disease, bronchial asthma, hemophilia, salicylate-sensitized people, pregnant or breastfeeding women and children under 12 years of age. It is effective and well tolerated when taken at the recommended dose (up to 4000 mg/day), and within a therapeutic dose range, it carries little to no risk of serious adverse events. Its mechanism of action is complex and includes the effects of both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway, cannabinoid system) anti-nociception processes and "redox" mechanism. Although paracetamol was discovered over 100 years ago and has been widely used in medical practice for more than half the century primarily due to its efficacy and safety profile.[17- 22]

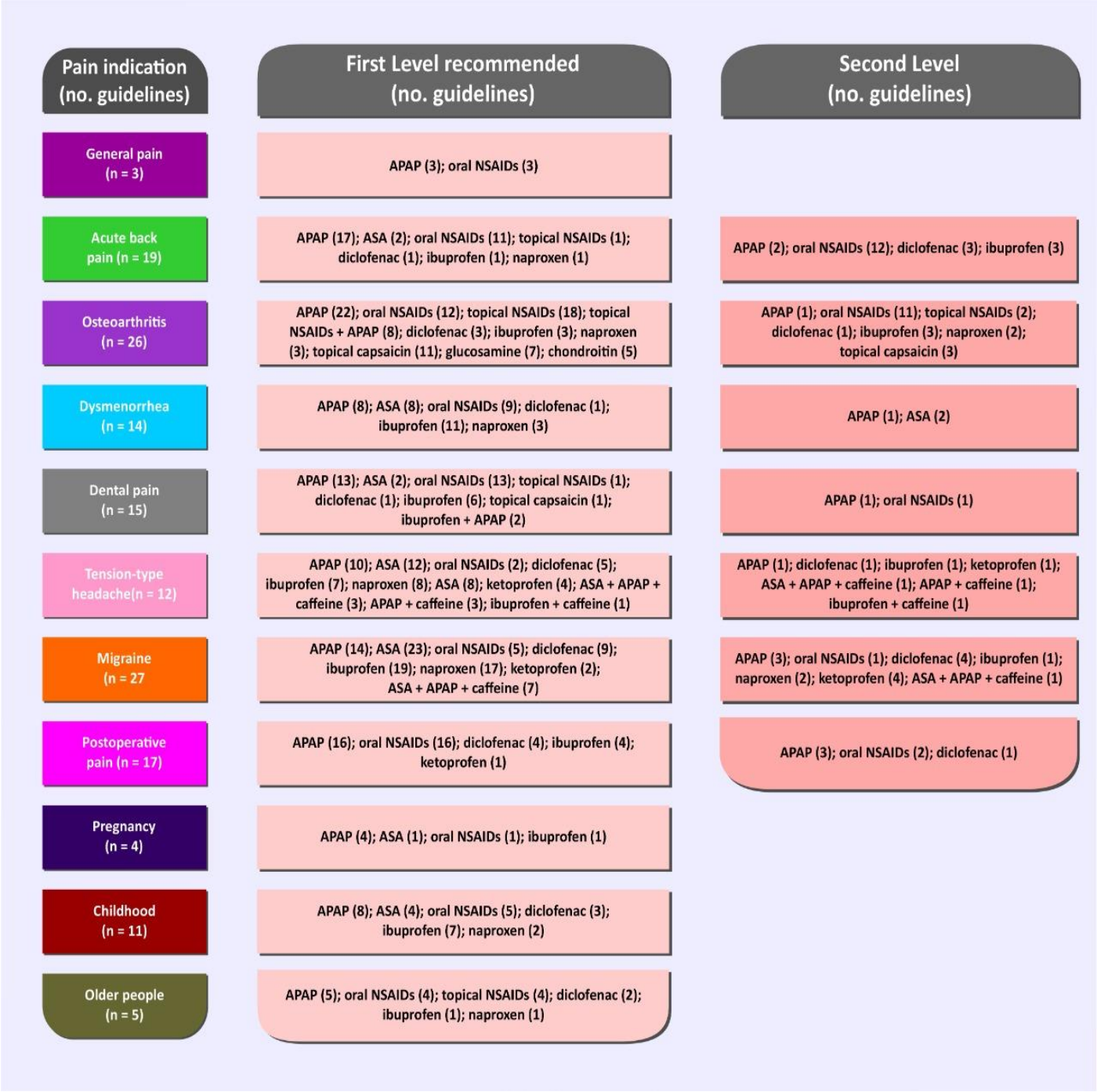

Figure no 1: Nonprescription pharmacological options recommended in treatment guidelines for the management of acute pain.

First level 1 = grade A, level I, or first choice; Second level = grade B, level II or second choice.[16]

Paracetamol is marketed under different trade names, as a single ingredient, and in combinations example, with tramadol, codeine phosphate, ascorbic acid, diphenhydramine hydrochloride as well as NSAIDs such as ibuprofen or propyphenazone for various

indications. Paracetamol is also available in various formats such as suppositories, tablets (uncoated, film-coated, effervescent), oral solution/syrup, powder for a solution - sachet, solution for infusion, etc.

Paracetamol is rapidly absorbed, and peak plasma concentrations (C_{max}) are attained at 0.5 - 1.5 hours (t_{max}) after intake of standard tablets or capsules after fasting. After oral administration of a 1000 mg conventional dose in adults, paracetamol is usually absorbed from the upper small intestine, gives a mean peak plasma concentration of 15–20 µg/mL within 30 to 120 min; mean systemic bioavailability is approximately 75%, the steady state obtained after five successive intakes at 6-hour intervals, the bioavailability is identical, whatever the unit dose used, within the range 325mg to 1g,[23]There is the first-passage effect, the significance of which varies according to the dosage or the number of doses, or both.[23]Paracetamol is predominately metabolized in the liver to form sulfate and glucuronide conjugates that are excreted in the urine, and only 2–5% of a therapeutic dose is excreted unchanged. Approximately 5–10% of the dose is converted to a potentially hepatotoxic intermediate, N-acetyl-para-benzoquinone imine (NAPQI). This is usually converted via glutathione to non-toxic mercapturic acid, which is then excreted via urine.[15]

After oral administration with these formulations, the clinical effect of paracetamol usually appears after 30 mins.[17]For standard solid dose paracetamol tablet formulations, the rate of absorption is dependent on the process of tablet disintegration and dissolution in the stomach and the rate of gastric emptying. Importantly, following oral administration, although it is rapidly and completely absorbed from the gastrointestinal tract, its systemic bioavailability is reduced by dose-dependent first-pass metabolism in the liver, such that the oral bioavailability may range from only 40–50% to 80–90%, depending on the dose and formulation. Reduced bioavailability may compromise the attainment of therapeutic circulating drug concentrations. Furthermore, paracetamol overdose is associated with a significant risk of hepatotoxicity. [15] The inter-patient variability, need for more consistent therapeutic effects and the possibility of the quicker onset of action had driven the development of faster-acting PCM formulations.[7, 24-28]

The faster-acting preparation of paracetamol, enriched with sodium bicarbonate which facilitates quicker dissolutions and enhances gastric emptying has shown in clinical studies to start their action within 15 min of intake. Due to this process, paracetamol quickly passes to the small intestine where it undergoes absorption (e.g., Panadol Rapid). The potential

drawback is the sodium content of this product (173 mg in each 500 mg tablet) which could have some implications for patients on a sodium-restricted diet.[17, 27]Rectal route of drug administration (suppositories), is another route that sometimes is used in the case of children. The bioavailability of paracetamol suppository is lower when compared to oral administration and the time necessary to achieve the therapeutic concentration is 120-180 min which is also significantly slower.[17]Other preparations such as sustained release have a slower rate of absorption, which is usually associated with its long presence in the body, i.e. with a longer duration of action, which in the case chronic pain complaints is of considerable importance.[17]

Paracetamol preparations available in India:

1. Conventional Paracetamol tablets

The conventional paracetamol tablet (500 mg, 650 mg, and 1000 mg) is widely available under various brand names and is the most commonly used preparation of paracetamol in India, as already mentioned above. The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus the onset of action is prolonged. This can be overcome by administrating the drug in liquid form but, many APIs have a limited level of stability in liquid form. After oral administration, paracetamol has a mean peak plasma concentration of 15–20 µg/mL within 30 to 120 min. The rate of paracetamol absorption from conventional formulations can be variable, which may result in a delayed or unpredictable therapeutic effect. Thus, this may not be the preferred formulation in case of emergencies or when a quick onset of action is required.[27]

2. Liquid paracetamol dosage forms

Liquid dosage forms are available under various brand names and were considered the most appropriate formulations for the pediatric population, as deemed easy to swallow without risk of choking and better for dose flexibility, catering for all age groups. In a study by Alessandrini et al in the European pediatric population, it was the most favorable dosage form for under 12 years and its preference began to decline from 13 to 18 years. However, more than a decade ago, it was recognized that liquid dosage forms present several drawbacks over solid medicines, such as extra palatability, exposure to undesirable excipients, stability challenges, and higher costs. Already in 2008, the World Health

Organization (WHO) was encouraging the use of flexible solid dosage forms as the preferred oral formulations for children, instead of liquid medicines.[29]

3. Oral dissolving paracetamol films

Available under the brand name *Molshil*, the orally dissolving film was recently made available in India. Fast-dissolving drug delivery is rapidly gaining interest in clinical research. These systems either dissolve or disintegrate, without needing water or chewing, generally within a minute. An important benefit is the accurate dosing as compared to liquid dosage forms, mostly used with pediatric patients, older patients, or in cases of dysphasia. Moreover, these systems may offer superior clinical profiles with potential oromucosal absorption, thus increasing the drug bioavailability concerning oral administration, especially in the case of drugs with higher first-pass metabolism.[30]

Advantages of Mouth Dissolving Films[30]

- A larger surface area promotes rapid disintegration and dissolution in the oral cavity.
- The better oral bioavailability of molecules that undergo first pass effect.
- Precision in the administered dose.
- Better patient compliance.
- Ease of swallowing and no need for water has led to better acceptability amongst dysphagic patients.
- Oral films are flexible and thus less fragile as compared to orally disintegrating technologies (ODT). Hence, there is the ease of transportation and consumer handling and storage.
- Mouth Dissolving Films are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs.
- Passing the first pass effect leads to a reduction of dose which can lead to a reduction in side effects associated with the molecules.

4. Paracetamol effervescent tablets

Available under the brand name of '*Fevadol'*and others as oral effervescent tables. The pharmacokinetic limitations of conventional paracetamol formulations may be largely

overcome by the use of effervescent formulations. According to the current European Pharmacopoeia, "Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates, which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration".[15, 30]

Effervescent paracetamol tablets contain as excipients an organic acid, typically citric or tartaric acid, and alkali metal carbonates or bicarbonates (typically sodium carbonate or bicarbonate). In the presence of water, the acid reacts with the carbonate/bicarbonate to form carbon dioxide: this creates turbulence that reduces the thickness of the boundary diffusion layer at the surface of the tablet, thereby enhancing the disintegration of the tablet and dissolution of the active principle. Citric acid is the acid most widely used in effervescent formulations, partly due to its pleasant citrus taste; other acids, such as tartaric or fumaric acids, are typically used only in small amounts, due to their low solubility in water. [15, 30]

Effervescence accelerates the disintegration of tablets, increases paracetamol dissolution, and renders the drug more hydrophilic in addition, effervescence increases gastric pH, thereby reducing drug contact time with the gastric mucosa and protecting the active drug from inactivation in the stomach. Together, these properties result in a faster onset of action. [15, 30]

Limitations: Because effervescent paracetamol formulations typically contain sodium bicarbonate, concerns have been expressed that, high levels of sodium in regular users of such preparations might trigger or exacerbate cardiovascular disorders, such as hypertension or heart failure, if taken regularly or in high doses.

5. Paracetamol with Optizorb technology

Optizorb is a patented dissolution technology, available in India only under the brand name - Crocin 650 and Crocin advance which is available globally in over 100 countries by GSK global as the brand name of Panadol with Optizorb technology. The Optizorb technology is proven to increase the speed of disintegration and dissolution of tablets in a patient's stomach, which leads to quicker paracetamol absorption. Pharmacokinetic (PK) studies done previously have shown that paracetamol with Optizorb technology is absorbed more rapidly and consistently than conventional paracetamol tablets. A scintigraphy study in human patients demonstrated faster disintegration/dissolution of paracetamol tablets with Optizorb technology, with full disintegration in 75% of patients within 5 minutes of ingestion.

Therefore, with proven fast tablet disintegration and fast absorption, paracetamol may be considered a good candidate for controlling fever & acute pain states. Combination of calcium carbonate and alginic acid, the super-disintegrator related to the fast disintegration/dissolution. Alginic acid in the aquatic medium, rapidly absorbs water and swells, while calcium carbonate was predicted to react with the acid in the stomach, quickly decompose and release API within 3 minutes. When the tablet comes in GIT, the super-disintegrants come in contact with digestive juices, which allows the tablet to decompose into smaller pieces from which the API could be more easily released compared with conventional paracetamol, it resulting in faster onset of disintegration (5 min in 75% of patients), significantly greater early exposure (25% faster to reach Tmax and 37% faster to reach therapeutic threshold), and within 10 mins of dosing, it can be detected in the plasma. Figure 2 shows the mean time in minutes for the onset of disintegration and complete disintegration of Crocin (paracetamol) with Optizorb technology compared to conventional paracetamol. [3, 27, 32]

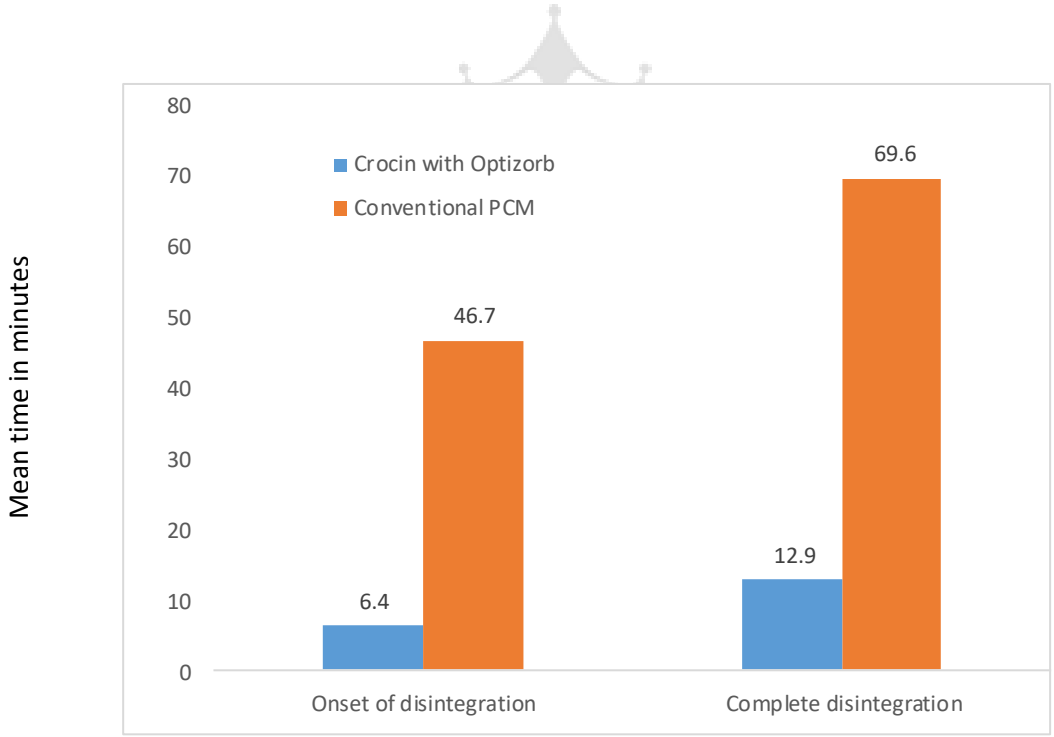

Figure no 2. Mean *in vivo* disintegration time for fast-dissolving Crocin with Optizorb versus conventional Paracetamol tablets[27]

In a study by Yue et al,[32] they compared conventional paracetamol tablets with fast-dissolving Crocin with Optizorb and measured the time to first perceptible pain relief confirmed by meaningful pain relief (TFPPRC); and time to meaningful pain relief (TMPR)

on postsurgical dental pain. Figure 3 demonstrates the results, which were significant for Crocin with Optizorbin in both parameters. Another parameter measured was the sum of pain relief and pain intensity differences from 0 to 6 hours (SPRID 6 Hours). SPRID was the sum of pain intensity difference (SPID) and total pain relief (TOTPAR) at each post-dosing time-point. SPRID score ranged from -1.8 (least pain relief) to 12.3 (highest pain relief). Table 1 shows the results for the same which were significant for Crocin with Optizorb when compared to conventional paracetamol.

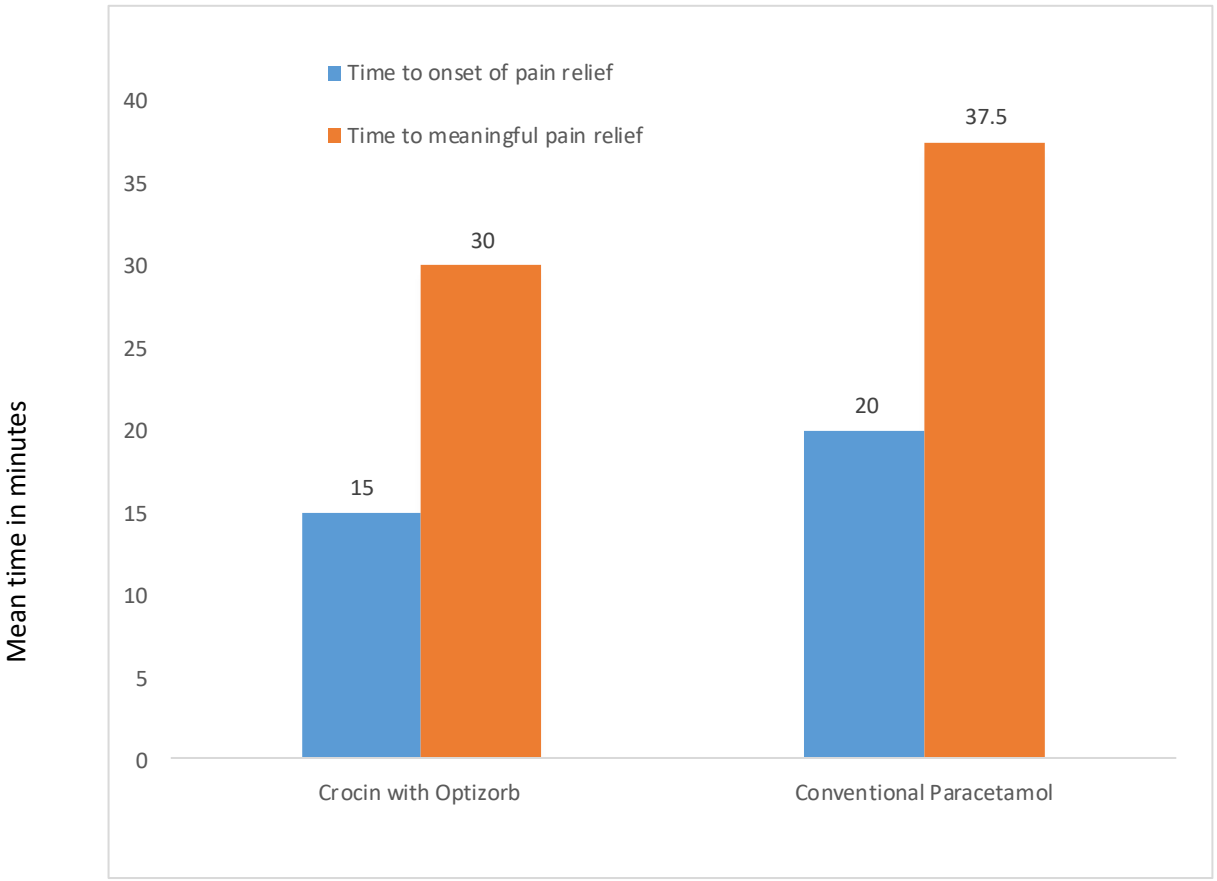

Figure no 3. Mean time of onset of pain relief and mean time of onset of meaningful pain relief for fast-dissolving Crocin with Optizorb versus conventional Paracetamol tablets[32]

Table 1. Sum of pain intensity and pain relief difference over 6 hours after the dose for fast-dissolving Crocin with Optizorb versus conventional Paracetamol tablets[32]

Time (hrs)	Crocin with Optizorb	Conventional paracetamol	Crocin with Optizorb vs Conventional paracetamol
	Adjusted Mean(SD)		Treatment Comparison
0-2	6.49(3.12)	5.55 (2.94)	0.93(0.30–1.57) P = 0.004
2-4	12.1 (6.94)	9.41 (6.19)	2.68(1.3–4.06) P = 0.0002
4-6	16.1 (10.68)	12.4 (9.89)	3.71(1.53–5.89) P = 0.0009

Advantages of Optizorb Technology[33]

- Provide quicker disintegration and dissolution, studies have concluded that it increased bioavailability and proved rapid absorption of drugs.
- Convenient for rapid dissolution and to produce rapid onset of action
- No chewing needed, improved compliance/added convenience
- Rapid drug therapy intervention
- Optizorb Technology can be administered to patients with stomach ulcers and pregnant women.
- No specific packaging is required can be packaged in push-through blisters, and is cost-effectively adaptable, and amenable to existing processing and packaging machinery.

Disadvantages of Optizorb Technology[33]

- Drugs with Optizorb Technology are hygroscopic so must be kept in a dry place.
- It also shows the fragile, effervesces granules' property.
- Produces carbon dioxide which can cause bowel problems.

6. Sustained release and bi-layer paracetamol

Sustained-release and bi-layered extended-release formulations have also been developed to reduce the frequency of intake; the latter combines both immediate and sustained-release paracetamol. One of the layers is formulated to obtain the immediate release of the drug, to reach a high serum concentration in a short period while the second layer is a controlled release hydrophilic matrix, which is so designed as to maintain an effective plasma level for a prolonged period, by releasing the drug at a slower rate. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at a steady state as the drug is released from the sustaining layer. This in turn promotes patient convenience and compliance.[34]

Limitations: It adds complexity and is comparatively expensive. There is the issue of insufficient hardness, layer separation, and reduced yield. Difficulty with inaccurate individual layer weight control. Possibility of cross-contamination between the layers which could lead to dosing failure or even toxicity.

Some of the other upcoming novel drug delivery systems in the pharmaceutical industry can be explored for the delivery of paracetamol in the future.

Nanostructures in oral drug delivery[2]

The versatility of using polymers in combination with nanotechnology has led to several innovative ideas for the miniaturization of oral drug delivery carriers for controlled release and targeting. Though there is various methodology, namely, micronization to improve drug dissolution, such techniques have a high failure rate for drugs with very low solubility. Several particulate carriers like nanoparticles, liposomes, micelles and microspheres, and solid lipid nanoparticles have been designed to overcome these limitations. Various natural polymers like albumin, gelatin, and alginate are used to prepare the nanoparticles, however, they have some inherent disadvantages like poor batch-to-batch reproducibility, prone to degradation and potential antigenicity. [2]

1. Polymeric Nanoparticle

Polymeric nanoparticles are prepared from biodegradable and biocompatible polymers with sizes ranging from 10 and 1000 nm, wherein the drug is dissolved, encapsulated, entrapped, or attached to a polymer nanoparticle matrix. Polymeric nanoparticles can be divided into two

main families: nanospheres, which have a homogeneous structure in the whole particle, and nanocapsules, which exhibit a typical core-shell structure: [2]

a. Nanospheres are spherical particles that can be crystalline or amorphous in nature as well as can protect the drug from enzymatic and chemical degradation.

b. Nanocapsules, due to their micronizing size, can be used as carriers for oral administration of enzymes, peptides, and proteins, however, they are restricted due to the GI barriers of the epithelium and by the degradation of digestive enzymes.

2. Polymeric Micelles (PM)

PM represents a promising delivery vehicle especially useful for poorly water-soluble pharmaceutical active ingredients to improve their oral bioavailability. The advantages of this system include their lower toxicity, small size, the advent of adverse reactions, and potentially long blood circulation times. One of the key issues of PMs is their stability in the physiological environment which may lead to side effects and adverse reactions. [2]

3. Nanocrystals

Drug nanocrystals are essentially nanoscopic crystals of the parent compound. By definition, they are less than 1 μm, but for practical purposes, they are often less than 500 nm. The advantages of nanocrystals include excellent reproducibility and applicability to a wide range of drugs with various solubility profiles. However, the nanocrystal approach sometimes requires high-energy input, which drives up the cost of production.[2]

4. Nanoemulsion

Nanoemulsions consist of two immiscible liquids, where one liquid acts as a continuous medium and the other as a dispersion medium of droplets in it. Advantages of nanoemulsion include high drug-loading capacity and the potential to increase permeability in the GI tract, thus increasing bioavailability. However, the lack of stability, with flocculation and coalescence often taking place during storage, and the lack of a controlled release mechanism is also a limitation.

5. Dendrimers

Dendrimers consist of a hydrophilic surface and hydrophobic core produced by convergent or divergent polymerization of branching units. These nanocarriers are formed by a central core

with branching polymers and peripheral functional groups. It facilitates the modulation of tight junctions and the integrity of cellular membranes, a major benefit for oral drug delivery. Dendrimers are capable of penetrating intestinal membranes preferably through lymphoid tissues, thus enhancing drug absorption. [2]

CONCLUSION:

Although paracetamol has been in clinical practice for over 60 years, it has a well-established risk-benefit profile and is consistently recommended in most national and international guidelines as first-line therapy as a prescription or non-prescription option for common pain conditions such as dental pain, migraine, acute back pain, postoperative pain, etc as well as an antipyretic. It also remains the drug of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAID), such as people with peptic ulcer disease, bronchial asthma, hemophilia, salicylate-sensitized people, pregnant or breastfeeding women and children under 12 years of age. But the various limitations faced with conventional paracetamol such as inter-patient variability, the need for more consistent therapeutic effects, and the possibility of a quicker onset of action, there was a need for the development of faster-acting paracetamol formulations to prevent delayed or unpredictable therapeutic effect and toxicities. Pharmacology has moved on from its earlier days to modern times with many new technologies being introduced and with the lack of availability of many formulations/technology in India to cater to these unmet needs, Crocin (paracetamol) advanced with Optizorb technology with its consistent therapeutic effects and faster disintegration time leading to a proven quicker onset of action is one such technology which is useful for its antipyretic action or acute/chronic pain relief. Although this is a relatively newer technology introduced in India, it would be beneficial for patients if its use becomes widespread as compared to conventional paracetamol tablets.

DISCLOSURE: All the authors are on the payrolls of Haleon/GlaxoSmithKline Asia Private Limited, India. Support in manuscript development has been provided by Dr. Salman Rizvi/Exicon consulting, India.

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