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Optimizing Control of Fever & Pain in Clinical Settings – An in-Vitro Investigation of the Dissolution and Disintegration Characteristics of Optizorb Technology in Acetaminophen Tablets versus Other Marketed Products

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ABSTRACT

Reduced inter-patient variability and consistent therapeutic effects are prerequisites in formulating drugs for reliable fever and pain control. The bioavailability of paracetamol is variable, leading to variable onset and duration of action. Optizorb technology incorporates a patented technology aimed at rapid dissolution and absorption of active ingredients, and improving the bioavailability of paracetamol. This study compared the dissolution of various paracetamol formulations versus the patented 'Optizorb' technology-based paracetamol tablets (Crocin Advance 650), determined the rate of disintegration in aqueous media and resultant changes in pH, and analyzed the residue profile. The dissolution test utilized media closely resembling the gastrointestinal environment (0.1N HCl, pH 5.8 phosphate buffered medium and pH 6.8 phosphate buffered medium). The disintegration test was performed using 1,000 mL of water as disintegration media. In 0.1N HCL, Crocin 650 mg tablets released 61% of the drug at 1-minute time interval, and 94% at the 3-minute time interval. The disintegration time for Crocin 650 was 48 seconds in water. Crocin 650 exhibited complete disintegration and dissolution in water, leaving no residues in the medium. Crocin Advance 650 with Optizorb technology ensures rapid, consistent drug release and may provide clinically relevant reduction in inter- and intra-patient variability and improved bioavailability.

KEYWORDS: paracetamol; analgesia; dissolution; disintegration; Optizorb

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INTRODUCTION

The management of fever and acute pain in clinical settings is a critical aspect of patient care,[1,2] demanding a judicious selection of pharmaceutical interventions.[3] Reduced inter-patient variability and consistent therapeutic effects are prerequisites in formulating reliable therapeutics.[4,5] Paracetamol (acetaminophen), a widely employed analgesic and antipyretic, is a water-soluble, odorless, white crystalline powder with a bitter taste. It undergoes efficient absorption from the proximal small intestine, substantially bypassing first-pass metabolism.[6] However, the variable bioavailability (63-89% in adults) may lead to unpredictable onset and duration of action.[6,7]

Reduced inter-patient variability is linked to uniform release and absorption of a drug, a process governed by the dissolution and disintegration properties, and gastric emptying time (GET).[8-10] The systemic absorption depends on dissolution under physiological conditions, and the rate of drug absorption affects the onset, intensity and duration of action.[11-13] Rapid drug absorption is crucial when a rapid onset of action is needed.[14] The absorption kinetics of paracetamol depend on the dynamics of gastric emptying.[10] Enhancing gastric emptying and gastrointestinal (GI) motility accelerate drug absorption.[14] Gastric mean residence time of paracetamol is 18.1 min at pH 7, and 46.7 min at pH 3, and the effect of pH is predominant over the volume of fluid.[15]

In the absence of complete disintegration of a tablet, only the surface active pharmaceutical ingredient (API) dissolves,

thus impacting clinical effectiveness.[9] Dissolution testing evaluates the rate at which the API dissolves from a tablet/capsule into a solution, simulating its behavior in the GI tract,[16] and is conducted under physiological conditions to enable meaningful interpretation (Figure 1).[17,18]

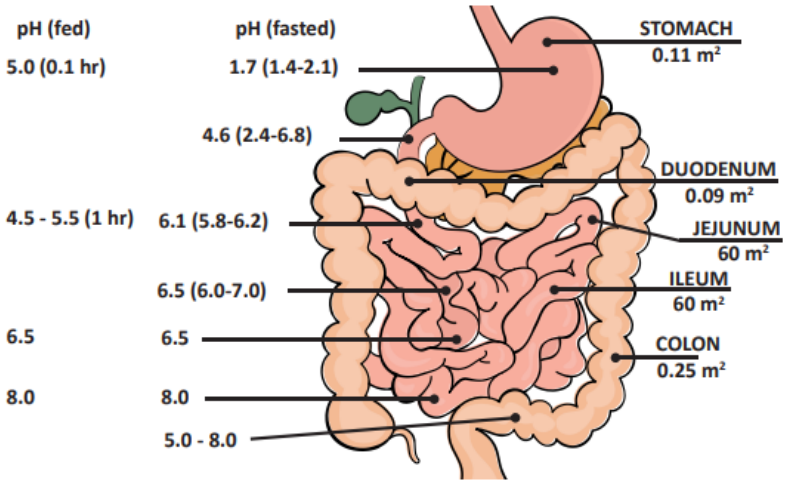


Figure 1. pH variation along the GI tract

GI: Gastrointestinal. The pH values refer to median quantities, and the range in parentheses refers to interquartile values. On the right are the approximated surface areas. Adapted from reference 18.[18]

Numerous paracetamol formulations are marketed, with varying excipients, manufacturing processes, and dissolution/disintegration profiles.[19] The patented Optizorb technology facilitates rapid dissolution and absorption of the API, and improves the bioavailability of paracetamol. It contains alginic acid that draws the fluid in surrounding aqueous media into the tablet, causing it to swell and break apart; calcium carbonate that works with alginic acid to boost the disintegration of the tablet; and crospovidone which acts as a super-disintegrant. Optizorb technology speeds up disintegration and releases near-complete API in 3 minutes, allowing quicker absorption and rapid onset of action.[20,21]
This study compared the dissolution and disintegration profile of Crocin Advance 650 with Optizorb technology against other paracetamol brands available in the market. The objective is to (i) compare the dissolution of various paracetamol formulations (ii) determine the rate of disintegration in aqueous media and resultant changes in pH (iii) analyze the residue profile.

METHODS AND MATERIALS

Study design

This experimental, *in vitro*, comparative pharmaceutical analysis was conducted at the Analytical Sciences Department, Sarvotham Care Ltd, Jeedipally India.

Chemicals/reagents used

Hydrochloric acid (Merck; grade: EMPARTA), potassium dihydrogen phosphate (Auantor; grade: AR), sodium hydroxide (Auantor; grade: AR) and reference standard acetaminophen (Sigma-Aldrich; purity: 99.98%).

Products tested

The different brands of paracetamol tested were Crocin Advance 650 mg with Optizorb technology, Dolo 650, Calpol 650, P 650, Fepanil 650, Pacimol 650, Pyrigesic, and Lanol ER. Haleon-owned and patented Optizorb technology is used by other marketed brands under agreement, and the results for such brands in India have not been included in this study.

Analytical procedures

The study strictly adhered to standardized and validated analytical methods, following established guidelines, including those stipulated by the United States Pharmacopeia (USP).

Dissolution testing

The dissolution test was performed using bio-relevant dissolution media. Acetaminophen is efficiently absorbed in the duodenum at pH 5.8. The dissolution test utilized three media closely resembling the GI tract environment per the parameters mentioned in Table 1.
Ten milliliters of sample volume from each bowl was withdrawn and replaced with the same volume of dissolution media at each time point. One milliliter of the sample was pipetted into 100 volumetric flasks, further diluted to volume with the diluent, and mixed. The ultraviolet (UV) absorbance of the resulting solution was measured at 243 nm wavelength using a UV-visible spectrophotometer. Before sample

measurement, a known concentration of paracetamol standard solution (~7.2 ppm) was measured at 243 nm wavelength.

Table 1. Parameters employed during dissolution testing

Dissolution media	0.1N HCl, pH 5.8 phosphate buffer, pH 6.8 phosphate buffer
Apparatus	Paddle
RPM	50
Media volume	900 mL
Temperature	37±0.5 °C
Time points	1 min, 3 min, 5 min, 10 min, 15 min, 20 min, and 30 min
Sample volume	10 mL

HCl: Hydrochloric acid; RPM: Rotation per minute.

Disintegration testing

The disintegration test for Crocin Advance 650 was performed using 1,000 mL of water at a bath temperature of 37±2.0°C. The time taken to disintegrate the tablet and pass through the mesh was recorded, and the mean time to disintegration was calculated.

Data analysis

Data analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). The variables analyzed included percent dissolution at time intervals of 1 min, 3 min, 5 min, 10 min, 15 min, 20 min, and 30 min; time to disintegration in water at bath temperature 37±2.0°C; pH of water before and after disintegration; visual residue analysis after disintegration and dissolution of the tablets in water at bath temperature 37±2°C.

RESULTS

Manufacturing details of the various brands studies are presented in Table 2.

Table 2. Manufacturing details of paracetamol brands analyzed in the study

Product	Batch no.	Label	Marketer/Manufacturer	Mfg. date	Exp. date
Crocin 650	EA22098	650 mg	Haleon	June 2023	May 2025
Dolo-650	D0BS3286	650 mg	Micro Labs	June 2023	May 2027
P-650	PST23026	650 mg	Apex Labs	Apr 2023	Mar 2026
Fepanil-650	FCTS23C11	650 mg	Aurobindo	Mar 2023	Feb 2026
Pacimol 650	GMW083018AK	650 mg	Ipca Labs	May 2023	Oct 2025
Lanol ER	HTR0123017	650 mg	Hetero drugs	May 2023	Apr 2025
Pyrigesic	DF2066	650 mg	East India Pharma	May 2022	Apr 2025

Overall dissolution profile for Crocin 650 in various media

In the 0.1% HCl media, 61% of the drug was released at the 1-minute interval, 27% was released in the pH 5.8 phosphate buffer media, and 22% was released in the pH 6.8 phosphate buffer media. At the 3-minute time interval, 94%, 63%, and 53% of drug was released in the 0.1% HCl media, pH 5.8 phosphate buffer, and pH 6.8 phosphate buffer, respectively. Drug release of over 92% was achieved in the phosphate-buffered media after 10 minutes, compared with 3 minutes for the 0.1% HCl media. The highest percentage of drug release (102%) was observed in the pH 5.8 phosphate buffer medium, surpassing the release percentages in the acidic media (98%) and pH 6.8 phosphate buffer medium (96%). Figure 2 describes the drug release characteristics in the different test media.

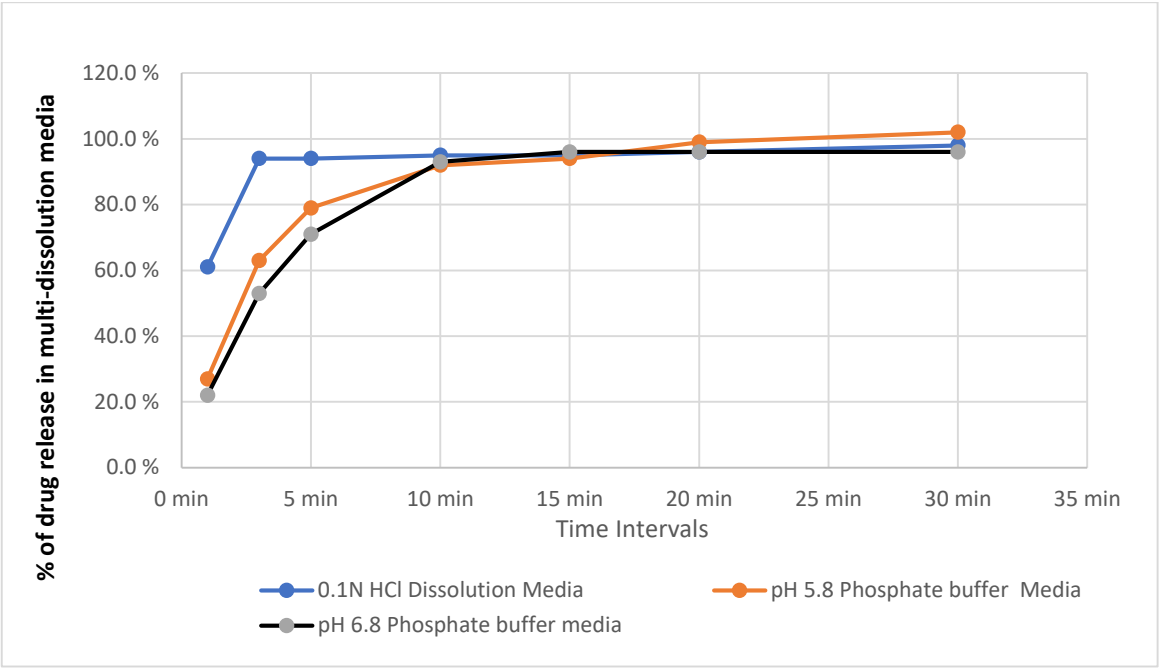


Figure 2. Graphical representation drug release of Crocin 650 mg tablets in various dissolution media

Comparison of Crocin 650 dissolution profile with other formulations

0.1N HCl dissolution media

Crocin 650 mg tablets showed strong release profiles compared with other media (Figure 3). Drug release was 61% at the 1-minute time interval, and 94% at the 3-minute time interval (Table 3). In contrast, drug release at 1 minute from Dolo 650 mg tablets was 29%, P 650 tablets was 25%, Fepanil 650 was 20%, Pyrigesic tablets was 28%, Pacimol 650 tablets was 11.0% and Lanol ER was 14.0%. Lanol ER Tablets released only 56% of drug content at 30 minutes, whereas Crocin 650 mg tablets and other products released ~100% of the drug. All drug products released over 85% of drug content at the 10-minute time intervals except Lanol ER (Figure 3, 4).

Table 3. Dissolution of Crocin 650 tablets in 0.1N HCl dissolution media

S. No.	1 min	3 min	5 min	10 min	15 min	20 min	30 min
1	51.0	91.0	91.0	93.0	93.0	94.0	95.0
2	690	93.0	96.0	94.0	96.0	96.0	98.0
3	58.0	95.0	92.0	94.0	94.0	94.0	96.0
4	70.0	93.0	94.0	95.0	95.0	97.0	97.0
5	52.0	92.0	94.0	95.0	96.0	97.0	990
6	63.0	97.0	96.0	97.0	98.0	99.0	100.0
Average	61.0	94.0	94.0	95.0	95.0	96.0	98.0
Minimum	51.0	91.0	91.0	93.0	93.0	94.0	95.0
Maximum	70.0	97.0	96.0	97.0	98.0	99.0	100.0

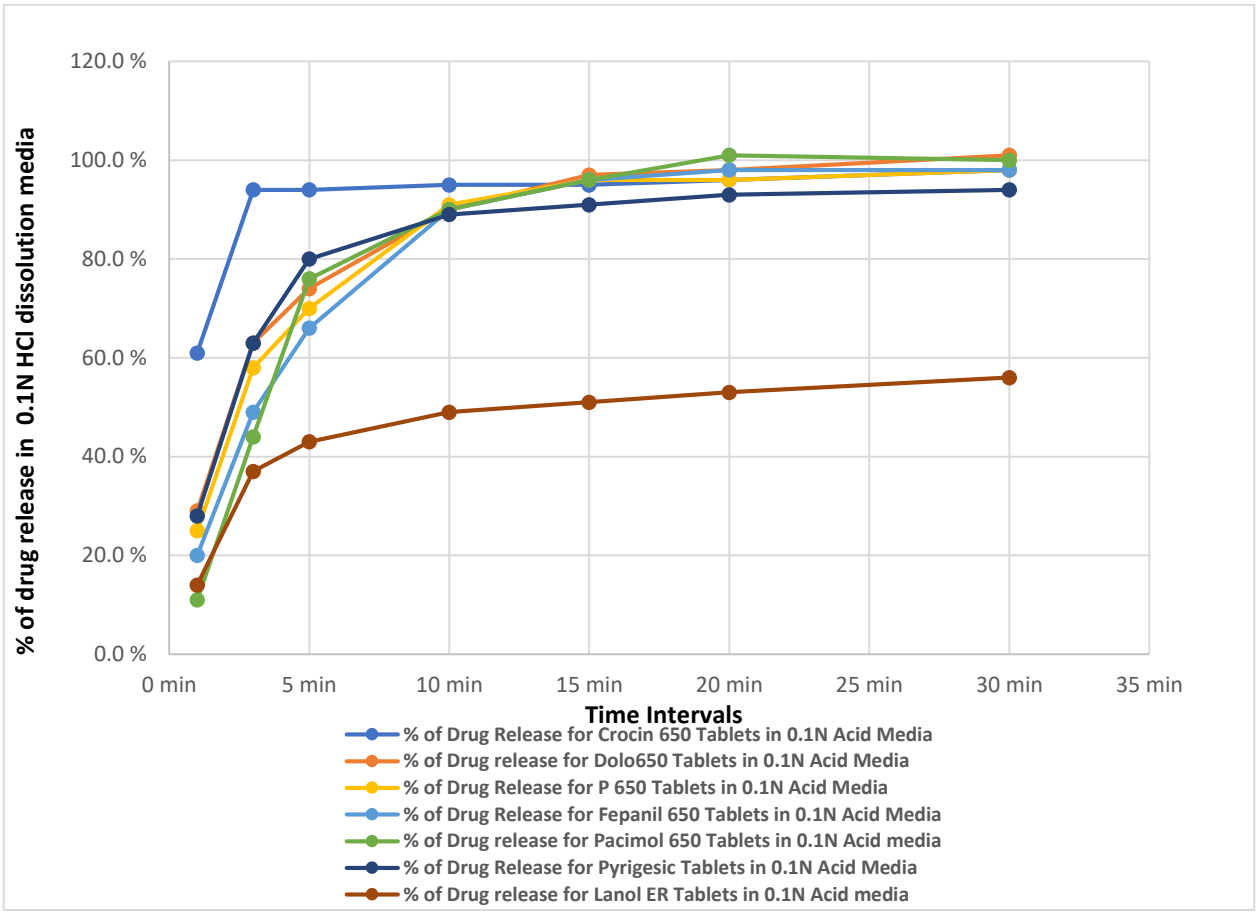


Figure 3. Drug release comparison of Crocin 650 mg tablets with other paracetamol brands in 0.1N acid media

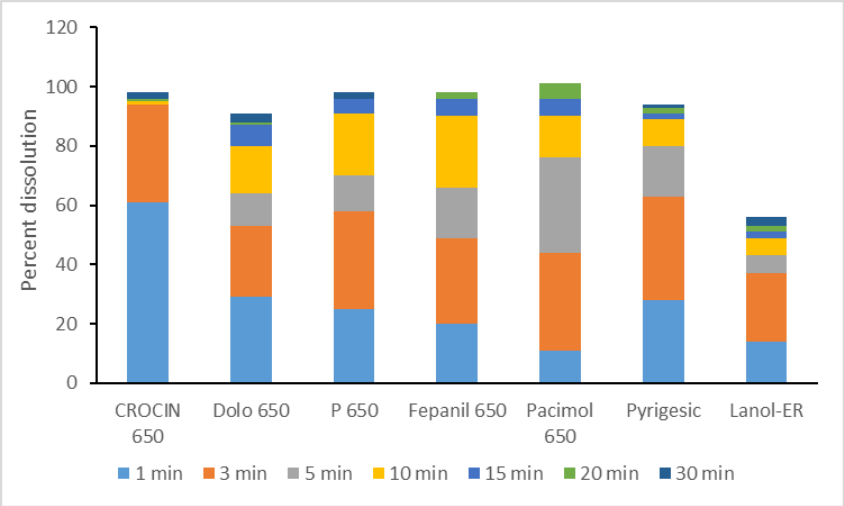


Figure 4. Comparison of percent dissolution at different time points

pH 5.8 phosphate buffer dissolution media

The proportion of drug release in pH 5.8 phosphate buffer media was similar for Crocin 650 and Dolo 650. Drug release at 15 minutes surpassed 85% for all formulations except Lanol ER (50%). Furthermore, Lanol ER achieved a drug release of 54% at the 30-minute interval, whereas drug release surpassed 90% for the remaining formulations (Figure 5).

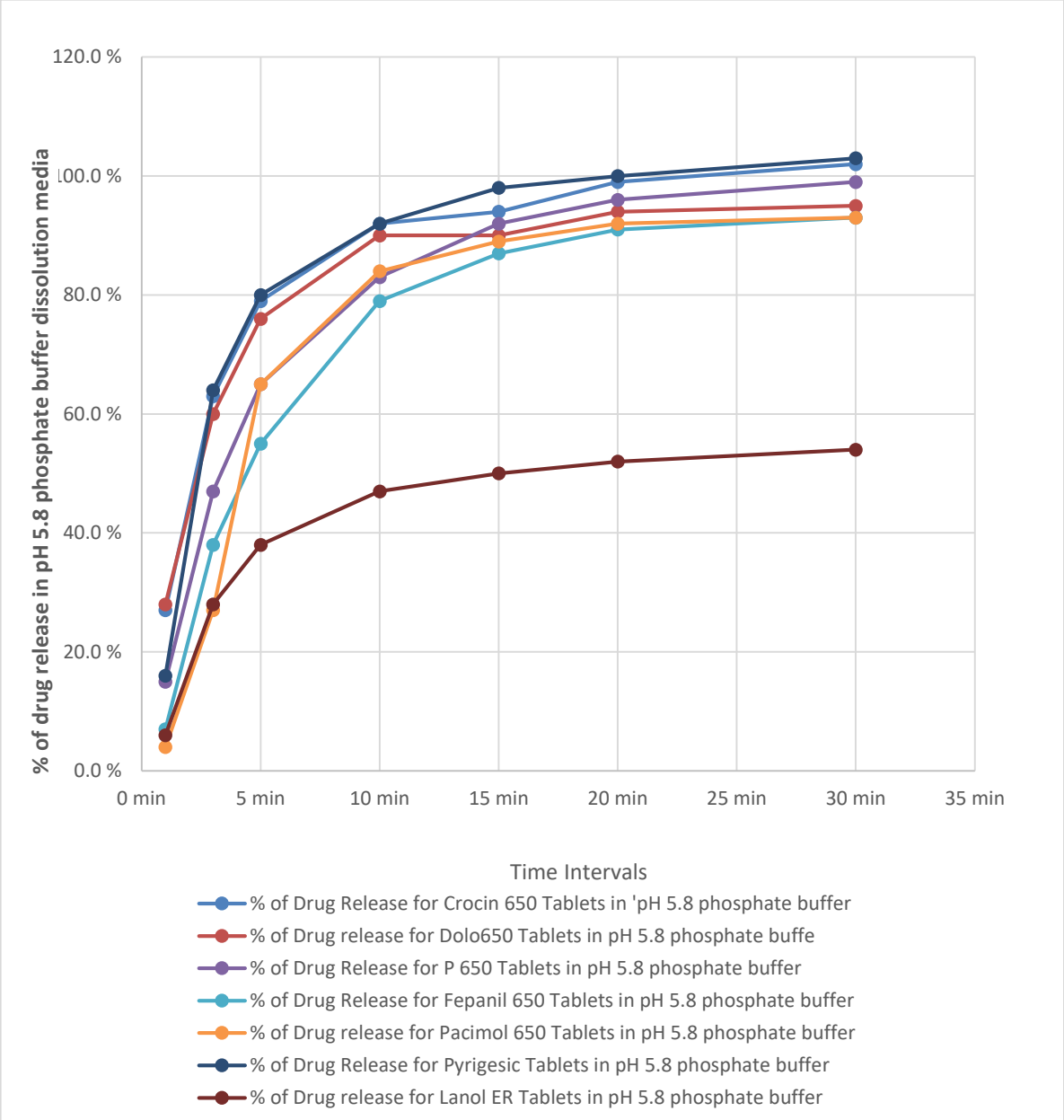


Figure 5. Drug release comparison of Crocin 650 mg tablets with other paracetamol brands in phosphate 5.8 buffer media.

pH 6.8 phosphate buffer dissolution media

Crocin 650 and other products (except Lanol ER and Pacimol 650 mg) showed similar drug release profiles at different time intervals. At the 10-minute interval, all products except Lanol ER released over 80% of drug content. At the 15-minute time interval, all products except Lanol ER tablets released over 90% of drug content (Figure 6).

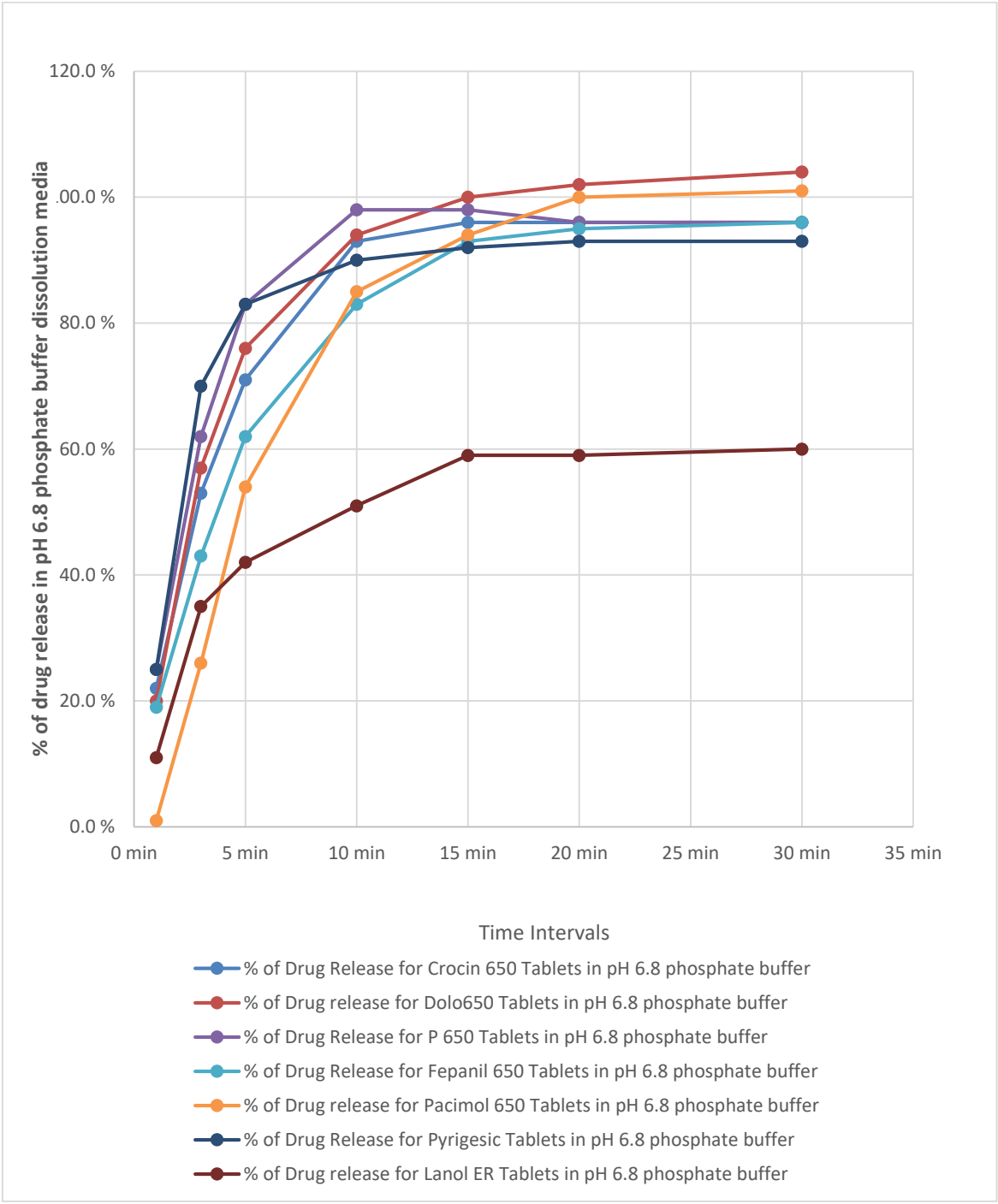


Figure 6. Drug release comparison of Crocin 650 mg tablets with other paracetamol brands in phosphate 6.8 buffer media

Disintegration time comparison of Crocin 650 and other paracetamol brands

Crocin 650 mg tablets and other products displayed varying disintegration times. The disintegration time for Crocin 650 (average tablet weight 861 mg) in 1,000 mL of water was 48 seconds. The pH of water before tablet disintegration was 5.4, while the pH of water after tablet disintegration was 7.81 (pH change of 2.41).

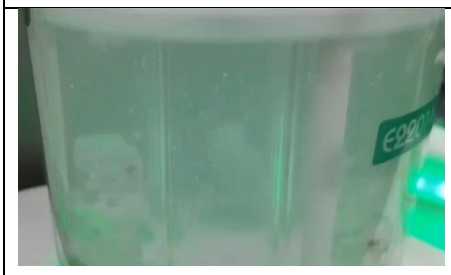
Tablet residue analysis

Crocin 650 exhibited complete disintegration and dissolution in water, leaving no residue in the medium. Figure 7 depicts images of residue analysis for all formulations tested.

Figure 7. Microscopic insight into tablet residue and drug release dynamics of Crocin 650 and other brands (A) Crocin 650 (B) Dolo 650 (C) Fepanil 650 (D) Pacimol 650 (E) Pyrigesic 650 (F) P-650) (G) Lanol ER

Crocin 650: Average tablet weight 861 mg (tablet was completely disintegrated and dissolved in the water; no tablet particles or residues were observed in the medium)

Dolo 650: Average tablet weight 823 mg (Tablet was completely disintegrated and no undissolved tablet particles were observed in the medium; more turbid solution observed in the medium)



Fepanil 650: Average tablet weight 734 mg (Tablet was completely disintegrated and small tablet particles or undissolved tablet particles or residues were observed in the medium)

Pacimol 650: Average tablet weight 730 mg (Tablet was completely disintegrated and more tablet particles or undissolved tablet particles or residues were observed in the medium)

Pyrigesic 650: Average tablet weight 743 mg (Tablet was completely disintegrated and some tablet particles or undissolved tablet or residues were observed in the medium)

P-650: Average tablet weight 802 mg (Tablet was completely disintegrated and some tablet particles or undissolved tablet or residues were observed in the medium)

Lanol ER: Average tablet weight 768 mg (tablet was not completely disintegrated)

DISCUSSION

The dissolution and disintegration tests with residue analysis for Crocin 650 mg tablets, including a comparison with other formulations, revealed significant insights.

The bioavailability of a drug depends on a number of factors including drug dissolution rate and solubility. Drug release and drug dissolution from the formulation are rate-limiting steps for the absorption of drugs from the GI tract. Of the media utilized in this study, 0.1N HCl media is considered most meaningful as it represents the gastric environment and the first environment to allow acid-led disintegration.

In this study, the choice of media significantly influenced the rate and extent of drug release from Crocin 650 tablets. In 0.1N HCl media, Crocin 650 mg tablets exhibited rapid

dissolution, achieving 61% drug release within 1 minute, and 94% within 3 minutes. The other formulations displayed a lower rate of drug release, resulting in lower bioavailability compared with Crocin 650.[22] Tablets with lower disintegration rates in the 0.1N HCl media may be expected to take additional time for complete disintegration or to disintegrate further in the small intestine. The rapid initial release may indicate the suitability of this formulation for dependable therapeutic outcome.[6,20]

At physiological pH, paracetamol is almost neutral, and is rapidly absorbed from the duodenum.[23] Optizorb technology increases the GET of paracetamol, leading to rapid absorption and increase in plasma concentration.[21] In this study, dissolution of acetaminophen increased the pH of the medium by 2.4 units. This increase in pH may facilitate gastric emptying.[15] Considering dissolution of 94% within 1 minute and the rapid gastric emptying, a significant proportion of the drug is available for absorption in the duodenum, where maximum absorption of acetaminophen occurs.[22] These properties of paracetamol with Optizorb technology could permit rapid, complete dissolution, and facilitate increased absorption in the small intestine, with improved therapeutic efficacy.[21] Crocin 650 tablets maintained a drug release of ~90% within 10 minutes in pH 5.8 and 6.8 phosphate buffer media, suggesting pH-dependent dissolution due to physicochemical, formulation-related, and physiological factors.[23]

In pH 5.8 and pH 6.8 phosphate buffer media, Crocin 650 and Dolo 650 displayed similar drug release profiles. The slight differences in the initial release (27% *vs.* 28% at 1 minute) may be attributed to formulation variations.[24] A study comparing *in vitro* drug release of paracetamol formulations reported drug release rates of 70-99.5%, with a significant variance in drug release (p-value <0.05). This finding underscores that different brands of paracetamol are not equivalent in their *in vitro* drug release performance.[6]

Varying disintegration times are attributed to formulation characteristics (excipients, super-disintegrants, and binders), manufacturing processes (compression force, tablet hardness, and coating thickness), and external factors (pH, temperature, and the presence of enzymes).[25] Disintegration plays a crucial role in increasing the bioavailability of a drug, leading to greater effective surface area exposed to GI fluids, and a higher drug dissolution rate. Disintegration times could affect clinical performance and patient experiences.[9]

This study reported a rapid disintegration of Crocin 650 within 48 seconds (in aqueous media), resulting in complete dispersion and dissolution of the tablet with no suspended particles or residues visibly observed. Coupled with the 98% drug release noted in 0.1N HCl media, it indicates that the Optizorb technology could be an ideal formulation that permits optimal disintegration and dissolution of the API. The rapid dissolution of Crocin 650 could be due to calcium carbonate and alginic acid which enhance tablet disintegration, and crospovidone, a super-disintegrant.[20] In contrast, undissolved tablet particles were noted in the medium for the other products tested. Lanol ER presented a unique drug release profile characterized by lower percentages of drug release, likely due to the extended-release formulation which is expected to behave different from rapid-release formulations.

The limitations of this study include the *in vitro* design which focuses on certain aspects of formulation design, and may not reflect the exact dissolution and disintegration behavior under physiological conditions. Hence, clinical correlations and judgment become important.

CONCLUSION

The performance of Crocin Advance 650 with Optizorb technology showcases its prowess in ensuring rapid and consistent drug release, and emphasizes its superior attributes in enhancing bioavailability, potentially expediting absorption, and delivering quick onset of action. Optizorb technology stands as a beacon for advancing pharmaceutical formulations, offering a significant stride toward optimizing therapeutic outcomes in clinical fever and pain management. Further research and *in vivo* studies may be necessary to establish a correlation between *in vitro* findings, clinical efficacy, and patient responses.

CONFLICT OF INTEREST

Asif Ali and Prashant Narang are presently on payroll of Haleon India (erstwhile GlaxoSmithKline Consumer Healthcare).

FUNDING SOURCE

The study was funded by Haleon India (erstwhile GlaxoSmithKline Consumer Healthcare), India.

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