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Effect of Beverages on Release of Paracetamol Tablet by *In-vitro* Dissolution Method Using Modified Media

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Oral route of drug delivery is one of the most preferred route of drug administration. People often consume oral solids, especially OTC drugs, at any time before or after breakfast with water or any other available hot or cold beverages. Crocin is one of the popular OTC brands of paracetamol, which is preferred in large number. Patient consumes this OTC tablet with available beverages which may be hot or cold. However, beverages interact with paracetamol, affecting the release of drug. In view of this, work was focused on study of the effect of various beverages such as coffee, tea, milk, carbonated drink and buttermilk on release of paracetamol (Crocin tablet) tablet using USP type II dissolution apparatus. Dissolution media used was modified phosphate buffer (pH 5.8) which was further added with beverages and was analyzed by UV spectrophotometrically. Dissolution profile revealed the maximum drug release 97.03 ± 1.29% in plain water was while minimum with tea 23.64 ± 2.00%. In conclusion, beverages consumed while administering with paracetamol tablet affects the release of drug and therefore should be cautiously used or avoided with dosage forms.

Keywords: Beverages; Crocin; paracetamol; tablet; dissolution profile.

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1. INTRODUCTION

Generally, over the counter drug products like tablets or capsules are taken with a glass of water. But in some cases, these dosage forms are ingested with beverages to aid swallowing or mask the taste of these pharmaceutical products [1]. In India, most common beverages consumed are tea, coffee, milk, buttermilk and carbonated drink. However, food drug interactions are well known and studied, the interaction with these beverages, which are common in India, is need to be studied in detail.

Over the counter products like paracetamol are very popular and commonly used for pain relief and to maintain elevated body temperature. The widely used brand of paracetamol is Crocin tablet®, which is consumed anytime with any available hot or cold beverages. However, the presence of these beverages changes the pH as well as temperature of dissolution media which ultimately affects the release of drug. In addition to this, drug may interact with the content of these beverages which further affects the drug release [1,2]. Thus, ultimately pharmacological action of drug is affected due to less absorption of drug. According to the literature survey, interaction studies between dosage form and beverages are focused on disintegration which simply tells us about the time required for the tablet to break down into smaller particles. However, the study based on dissolution behavior is not yet performed. In view of this, the current work was focused on study of the effect of various beverages such as coffee, tea, milk, carbonated drink and buttermilk (hot and cold beverages) on release of paracetamol (crocin tablet) tablet using USP type II dissolution apparatus. Dissolution media used was modified phosphate buffer (pH 5.8) which was further added with beverages and was analyzed by UV spectrophotometrically. Thus, drug release profile of paracetamol tablet was focused in presence of various commonly consumed beverages.

2. MATERIALS AND METHODS

2.1 Materials

Paracetamol was obtained from Shri-Krishna Pharmaceuticals whereas Crocin tablets manufactured by GlaxoSmithKline Pharmaceuticals Ltd. was purchased from Sohit Medical Store Bavdhan (Batch No: R15185). Other beverages such as milk, tea, coffee, carbonated drink and buttermilk were purchased locally.

2.2 Methods

2.2.1 Evaluation parameters of Tablet

2.2.1.1 Weight variation test

Accurately, 20 tablets were weighed individually. The average weight of each tablet and deviation were calculated using IP 2010.

2.2.1.2 Friability test

Friability test was carried out on 10 pre-weighed tablets by placing them in Roche friability apparatus at 100 rpm. Percent weight loss was calculated after reweighing the tablets.

2.2.1.3 Disintegration test

Time taken for the tablet to break down into smaller particles was calculated by using disintegration apparatus (LAB India, DS-8000) A tablet was placed in each of 6 tubes containing distilled water at 37ºC ±1 as disintegrating medium. The basket ascended and descended through a distance of 5cm to 6cm at a frequency of 280 to 320 cycles per minute. Time at which all particles disintegrate was recorded.

2.2.1.4 Hardness test

Five tablets were subjected for hardness testing and crushing strength of tablet was measured using Monsanto hardness tester.

2.2.2 Preparation of phosphate buffer (pH 5.8) solution

Accurately weighed quantity of 27.1gm of potassium dihydrogen phosphate was dissolved in 1000ml distilled water to make 0.2M solution (solution A). Likewise, 4gm of sodium hydroxide was dissolved in 500ml distilled water (solution B).Solution A (500 ml) and solution B (72 ml) were mixed and volume was made up to 1000ml with distilled water to get pH5.8 buffer [2].

2.2.3 Calibration curve

The standard stock solution was prepared by dissolving 25mg standard paracetamol in 25 ml distilled water. Further dilutions were made to get 5, 10, 15, 20 and 25ppm solutions. The calibration curve was constructed by recording absorbance of these solutions [3].

2.2.4 Dissolution study using modified phosphate buffer (pH 5.8)

Dissolution study was carried out using USP Type II apparatus [3] (LAB India, DS-8000) with 900ml media at 37±0.5ºC, 50 rpm. Crocin tablet (500mg of paracetamol) was introduced into vessel. The aliquots of samples were withdrawn periodically at 15 min interval time and replaced with same volume of media which was maintained as blank medium. The samples were filtered through Whatman filter paper (pore size 0.3 µm) using a vacuum filter pump and analyzed after suitable dilution using UV spectrophotometer (Cary 100, Varian) at 243 nm. The above process was performed separately for each beverage viz. water, milk, tea, coffee, carbonated drink and buttermilk. Each time 200ml of beverage was added to 700ml of phosphate buffer (5.8) which was used as a dissolution media. The temperature of beverages such as carbonated drink and buttermilk while adding to media was 20ºC, while tea, coffee and milk was 50 ºC. Each process was coded as D0 (plain dissolution without any beverages), DW (dissolution with 200ml water), DM (dissolution with 200 ml milk), DT (dissolution with 200 ml tea), DCo (dissolution with 200 ml coffee), DCd (dissolution with 200 ml carbonated drink), DB (dissolution with 200 ml buttermilk),

2.2.5 Dissolution study using modified simulated gastric fluid

Dissolution study was carried out using USP Type II apparatus [3] (LAB India, DS-8000) with 900ml simulated gastric fluid (0.1N HCl) media at 37±0.5ºC, 50 rpm. Crocin tablet (500 mg of paracetamol) was introduced into vessel. The aliquots of samples were withdrawn periodically at 15min interval time and replaced with same volume of media which was maintained as blank medium. The samples were filtered through Whatman filter paper (pore size 0.3µm) using a vacuum filter pump and analyzed after suitable dilution using UV spectrophotometer (Cary 100,Varian) at 243nm. The above process was performed separately for each beverage viz. water, milk, tea, coffee, carbonated drink and buttermilk. Each time 200 ml of beverage was added to 700ml of simulated gastric fluid (1.2) which was used as a dissolution media. The temperature of beverages such as carbonated drink and buttermilk while adding to media was 20ºC, while tea, coffee and milk was 50ºC. Each process was coded as D0 (plain dissolution without any beverages), DW (dissolution with 200 ml water), DM (dissolution with 200 ml milk), DT (dissolution with 200 ml tea), DCo (dissolution with 200 ml coffee), DCd (dissolution with 200 ml carbonated drink), DB (dissolution with 200 ml buttermilk).

3. RESULTS AND DISCUSSION

3.1 Evaluation of Tablets

Weight variation is a valid indication of variation in drug content. According to USP, the acceptable deviation should not be more than 5%. As shown in Table 1 Crocin tablet comply with weight variation test. Disintegration time of Crocin tablet was 10mins which complies with USP. Disintegration is breaking down of particles and it is the first step in dissolution. Friability results are shown in Table 1. The difference in weight of tablet before and after the test was 0.1% and it was within the acceptable limit. The Hardness Test is a measure of compression force required to break the tablet. The hardness of the tablet was found satisfactorily in the prescribed range. No significant deviation was observed in average thickness and diameter. The percent assay of Crocin tablet was found to be 103% and complies with the requirement of USP.

Table 1. Physiological parameter of tablet

Tablet	Weight (g)	Friability (%)
Crocin	661.5 ± 0.02	0.1 ± 0.02

Values are expressed in mean ± standard deviation

3.2 Calibration Curve Studies

Calibration curve was plotted using UV. Data of these studies is shown in Fig. 1.

3.3 Dissolution Studies of Paracetamol in Solvents and Beverages (Phosphate Buffer 5.8)

Drug release using tea, coffee, milk, buttermilk, and carbonated drink as dissolution medium is shown in Fig. 2. Drug release of paracetamol in phosphate buffer solution D0 was found to be 86.36 ± 2.30 % at 90 min and 93.43 ± 1.11 % at 120 min, while the release of drug in water DW was 95.7± 1.23 % at 90 min and 97.03± 1.29 % at 120 vmin.

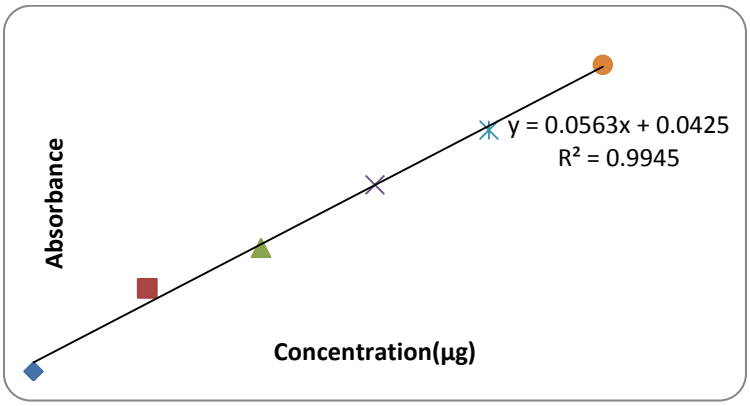

Fig. 1. Calibration curve by UV

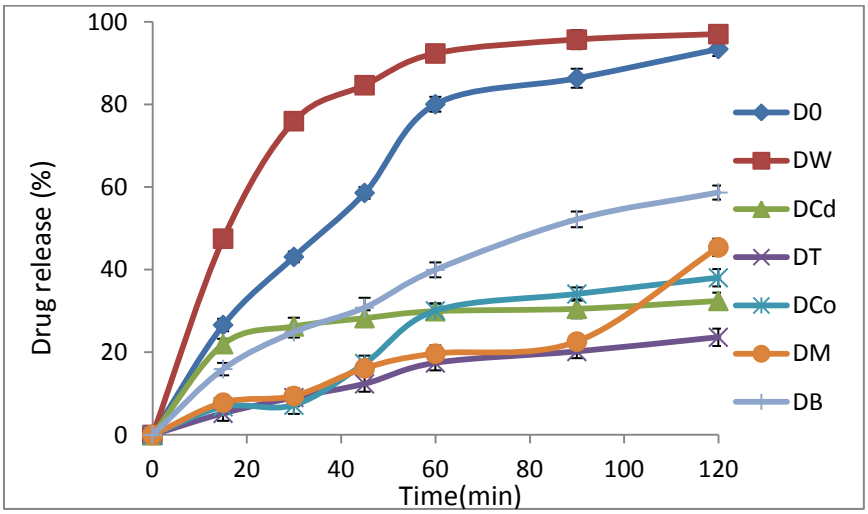

Fig. 2. Dissolution profile of paracetamol in various beverages by UV analysis (modified media pH 5.8)

3.4 Drug Release in Beverages

Drug release of paracetamol in phosphate buffer (700ml) + beverages (200ml) was found to be as follows:

3.4.1 Drug release in phosphate buffer (700 ml) + Tea (200 ml) DT

Drug release of paracetamol in phosphate buffer (700 ml) + tea (200 ml) DT was found to be as follows: 9.05 ± 1.10 % at 30 min, 17.43 ± 1.25 % at 60 min, 20.19 ± 1.82 % at 90 min, 23.64 ± 2.00 % at 120 min. change is pH does not retard the dissolution of paracetamol [4]. DT showed even lesser amount of drug release as compared to D0, DW and DCd. Even after 120 min, total amount of drug release was much less than DCd. Here, prepared tea contained caffeine, theobromine, theophylline, tannins (polyphenols), gingerol (from ginger), lactose, calcium, fats (from milk).Tea contains proteins, carbohydrates, minerals, tannins, phenolic compound and lipids. The tannic acid in tea might reduce the dissolution of drug by forming complex with paracetamol. Paracetamol containing formulation showed delayed disintegration in milk [5] by 21-27 min longer than in water. It is recently reported that food could significantly delay tablet disintegration in the stomach by the formation of the film around the tablet, which depend on the excipients of the tablet and composition of administered food. Presence of proteins in the food also affects the disintegration of the tablet [6]. Tea is prepared using milk and tea powder, therefore, milk might be delaying the disintegration of Crocin tablet in phosphate buffer and tea medium and ultimately delaying the dissolution of paracetamol. The polyphenols present in tea reacts with the protein components of milk and form complex [7]. This complex might be adsorbing paracetamol and retarding the dissolution of paracetamol in the dissolution medium.

3.4.2 Drug release in Phosphate buffer (700 ml) + carbonated drink (200 ml) DCd

Drug release of paracetamol in phosphate buffer (700ml) + carbonated drink (200ml) DCd was found to be as follows: 26.28 ± 1.44% at 30 min, 28.28 ± 1.01 % at 45min, 29.97 ± 1.90% at 60min, 30.54 ± 2.00% at 90min, 32.45 ± 1.22% at 120 min. DCd showed very less amount of drug released since start of the dissolution process as compared to D0 and DW. Even after 120 min, total amount of drug release was very less. Here, carbonated drink consisted of caffeine citrate, citric acid, vanilla extract, lime juice, sugar, coca leaves extract, caramel, water and flavoring agent. The content of drink was found to interact with paracetamol, which resulted in retarding the release of paracetamol.

3.4.3 Drug release in Phosphate buffer (700 ml) + coffee (200 ml) DCo

Drug release of paracetamol in phosphate buffer (700ml) + coffee (200ml) DCo was found to be as follows: 7.20 ± 1.21 % at 30min, 30.06 ± 1.29 % at 60min, 34.12 ± 1.07 % at 90min, 38.06 ± 1.05 % at 120min. Coffee contains caffeine, ash, carbohydrates. Caffeine and paracetamol might interact with each other due which absorption of drugs in retarded in coffee. However, DCo exhibited better release of paracetamol than tea. The release in the coffee containing medium was also less than the milk containing a medium. At 15 min the release of Paracetamol in milk medium was 17.62%. Coffee also contains tannins and these tannins forms complex with milk [7]. This complex will be retarding the release of Paracetamol from the Crocin tablet. The coffee powder contains more caffeine than tea powder so, caffeine might be interfering in the Paracetamol release and so the release of Paracetamol at 120 min in coffee containing medium is 38.06 ± 1.05 %. Coffee also contains chlorogenic acid and which is not present in tea. Chlorogenic acid is a polyphenolic compound, which is an ester of caffeic acid and quinic acid. This polyphenol might be retarding the release of Paracetamol. The viscosity of the milk is also responsible for the slow dissolution of the Paracetamol in the milk [8].

3.4.4 Drug release in Phosphate buffer (700ml) + milk (200ml) DM

Drug release of paracetamol in phosphate buffer (700ml) + milk (200ml) DM was found to be as follows: 9.43 ± 1.06% at 30min, 19.67 ± 1.62% at 60min, 22.60 ± 1.29 % at 90min, 45.41± 1.66 % at 120min. As compared to D0 and DW, drug release with milk beverage was found to be less, while than tea and coca-cola. Milk contains fats, proteins, vitamins and minerals, and lactose. Proteins and calcium carbonate in milk may cause a chemical reaction with drug. Kalantzi et al. have reported that dissolution of Paracetamol from tablets significantly slower in milk [6]. Presence of carbohydrate in the milk interacts with many drugs and retards their absorption [9]. So carbohydrate of milk might also be interacting with Paracetamol and affecting its dissolution. Calcium and casein content of milk is also reported to interact with many drugs and reduces the bioavailability of drugs. These components of milk might also be responsible for the less dissolution of paracetamol in phosphate buffer-milk medium.

3.4.5 Drug release in Phosphate buffer (700ml) + buttermilk (200ml) DB

Drug release of paracetamol in phosphate buffer (700ml) + buttermilk (200ml) DB was found to be as follows: 24.89 ± 1.20 % at 30min, 39.97 ± 1.54 % at 60min, 52.19 ± 1.56 % at 90min, 58.62 ± 1.88 % at 120min. Though, DB showed less drug release than D0 and DW, but was more than DT, DCd, DCo and DM. Buttermilk contains fats, proteins, carbohydrates, copper, zinc and ferrous which may interact with paracetamol release. Buttermilk contains more amount of water and viscosity of it is less so the dissolution of the drug might be more in phosphate buffer-buttermilk compared to another medium. Buttermilk has low viscosity, high emulsifying capacity due to the presence of phospholipids and low foaming capacity compared to milk [10]. These factors might be responsible for higher solubility of paracetamol.

Thus, dissolution profile showed that release of paracetamol is highly affected by the type of beverage consumed during administration of drug [11]. The order of release of paracetamol from lowest to highest was as follows: tea, carbonated drink, coffee, milk and buttermilk. Thus, the study revealed that paracetamol tablet must be administrated with water as a vehicle.

3.5 Dissolution Studies of Paracetamol in Solvents and Beverages (Simulated gastric fluid 1.2)

Drug release using tea, coffee, milk, buttermilk, and carbonated drink as dissolution medium is shown in Fig 3. Drug release of paracetamol in

phosphate buffer solution D0 was found to be 78.90 ± 1.90 % at 90 min and 93.06 ± 1.10 % at 120 min, while the release of drug in water DW was 77.60± 1.40 % at 90 min and 90.09 ± 1.60 % at 120min.

3.6 Drug Release in Beverages

Drug release of paracetamol in phosphate buffer (700ml) + beverages (200ml) was found to be as follows:

3.6.1 Drug release in Phosphate buffer (700ml) + Tea (200ml) DT

Drug release of paracetamol in phosphate buffer (700ml) + tea (200ml) DT was found to be as follows: 10.10 ± 0.70 % at 30 min, 19.80 ± 1.00 % at 60min, 21.90 ± 1.10 % at 90 min, 22.10 ± 1.20 % at 120min. change is pH does not retard the dissolution of paracetamol

3.6.2 Drug release in Phosphate buffer (700 ml) + carbonated drink (200 ml) DCd

Drug release of paracetamol in phosphate buffer (700ml) + carbonated drink (200ml) DCd was found to be as follows: 23.18 ± 1.20 % at 30min, 27.10 ± 1.10 % at 45min, 29.08 ± 0.80% at 60min, 34.10 ± 1.10 % at 90min, 35.20 ± 1.10 % at 120min.

3.6.3 Drug release in Phosphate buffer (700ml) + coffee (200 ml) DCo

Drug release of paracetamol in phosphate buffer (700ml) + coffee (200ml) DCo was found to be as follows: 9.43 ± 0.80 % at 30min, 30.00 ± 1.10 % at 60min, 34.10 ± 1.10 % at 90min, 38.90 ± 1.10 % at 120min.

3.6.4 Drug release in Phosphate buffer (700ml) + milk (200ml) DM

Drug release of paracetamol in phosphate buffer (700ml) + milk (200ml) DM was found to be as follows: 10.12 ± 0.60 % at 30min, 22.18 ± 1.90 % at 60min, 25.10 ± 1.10 % at 90min, 45.00± 0.10 % at 120 min.

3.6.5 Drug release in Phosphate buffer (700ml) + buttermilk (200ml) DB

Drug release of paracetamol in phosphate buffer (700ml) + buttermilk (200ml) DB was found to be as follows: 23.90 ± 1.10 % at 30min, 39.97 ± 0.30% at 60 min, 52.10 ± 0.20 % at 90min, 57.10 ± 0.90% at 120 min.

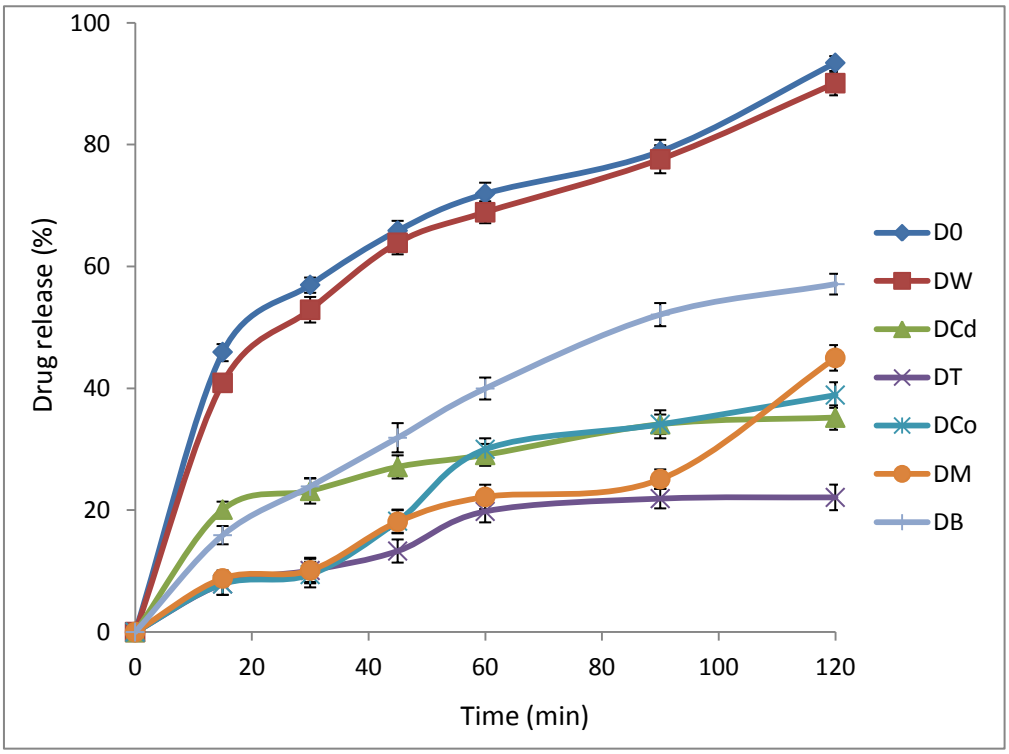

Fig. 3. Dissolution profile of paracetamol in various beverages by UV analysis (modified simulated gastric media pH 1.2)

4. CONCLUSION

Paracetamol, a widely used OTC drug, is consumed with variety of vehicles and beverages. The study revealed the interaction of paracetamol with the contents of beverages, which ultimately resulted in slowing down the process of dissolution and drug release. Drug release in modified media pH 5.8 and modified media of simulated gastric juice was found similar. Thus, beverages consumed while administering with paracetamol tablet affects the release of drug and therefore should be cautiously used or avoided with dosage forms. Therefore, in conclusion, paracetamol tablet must be administered with a glass of water for better dissolution and required therapeutic action of drug.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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