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RESEARCH ARTICLE

Study of Altered Disintegration Behavior of Immediate Release Pain Medication in Different Beverages

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ABSTRACT

Variable drug release from the solid dosage forms has been an important cause of bioavailability problems. The two main processes by which they release drugs are disintegration and dissolution. This study compared the disintegration times and *in vitro* dissolution behaviour of three immediate-release pain-relief tablets, diclofenac, aceclofenac, tramadol HCl. In different beverages were compared with water beverages like whole milk, low fat milk, coco-cola, tropicana juice, iced coffee, butter milk the test was carried out using USP disintegration test apparatus results showed that the disintegration time was highest in 6% milk then in 3.5% milk, subsequently followed by fruit juices and butter milk .the disintegration was the least in the soft drink. From the above study it can be concluded that there is a variation in the disintegration time of the pain relief tablets in different beverages. The highest variation was found when milk was the beverage. The patients on these medications should be advised against consuming them with beverages slowing their disintegration and in turn affecting their bioavailability.

KEYWORDS

Bioavailability, Beverages, *In vitro* disintegration

INTRODUCTION

Oral solid dosage forms such as tablets and hard-gelatin capsules, which have been inexistence since the nineteenth century, remain the most frequently used dosage forms today. Drug substances most frequently are administered orally by means of solid dosage forms like tablets and capsules Tablets and capsules accounted for about half of the 579 new medicines licensed from 1995 to 1999[1]. A tablet that can withstand the stresses of subsequent packaging operations and reach the patient in an acceptable condition is generally assessed by friability and hardness tests.

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Disintegration is one of the important physical properties of a tablet dosage form during the research and development stage and is most commonly studied in either water or simulated gastric medium and occasionally in simulated intestinal medium. However, commonly patients do take medications with beverages other than water. Often patient's are counselled to take medications, especially pain-relief medications, with milk to decrease the potential for gastric irritation.

Tablets are used mainly for systemic drug delivery and also for local drug action. For systemic use the drug must be released from the tablet that is normally dissolved in the fluids of the mouth, stomach or intestine and thereafter be absorbed into the systemic circulation, by which it reaches its desired site of action[2]. The term 'bioavailability' is used to describe the

fraction of drug dose which reaches the systemic circulation unchanged. Many of the factors which influence bioavailability can be changed by food, both 'acutely', if a drug is taken with a meal, and 'chronically', where regularly consumed food items influence drug disposition. The nature of these interactions is complicated, and is influenced by the quantity and composition of food. It should also be noted that in addition to changing the pharmacokinetics of some drugs, food can also alter their pharmacodynamic effects [3].

Recent advances in pharmaceutical technologies, polymer sciences and analytical tools have enabled design of smarter drug delivery systems. Various formulation strategies are employed for optimizing the therapeutic efficiency and/or minimizing side effects of drugs designed as smart dosage forms. Such techniques used for extended release or programmed release or targeted release has generated many patents. They not only offer the manufacturers an edge above the competitors but often offer obvious advantages to the patients also due to reduced dose frequency, reduced total dose consumption and minimal exposure of the non-target tissues to pharmacological effects. Most of the patients traditionally consume the medicines with one or more of the beverages including the health drinks with complex compositions. It is known fact that there is a great variation in the quantity and the regimen followed for consumption of these beverages. Here are possibilities of probable interactions between any of the components of these beverages and the formulation ingredient including the drug candidate. Such interactions have so far been neglected and only a few like those with the grapefruit juice have been reported. A few reports also cite the dramatic alterations in the release profiles of commonly used OTC type drugs due to concomitant consumption of alcoholic beverages. Unlike the drug-drug or food drug interactions however, the data available on probable drug –beverage interactions is very limited. Classically any of the interactions can be classified as follows; Drug-Drug Drug –Food Drug- Chemical Drug-Disease the net effect of any type of drug interaction is generally, Quantitative i.e. increased or decreased therapeutic response Rapid or slower effect Precipitation of newer or increased adverse-effects.

Most of these adverse reactions alter the efficacy of drug e.g. Tetracycline when concomitantly administered with food, antacid or mineral supplements containing metal ions. Moreover, such adverse interactions may offset the advantages of drug delivery from specially designed formulations which act as smart delivery systems. Hence, there is great need to explore the possible drug-beverage interactions and develop tools to elucidate their probable mechanisms. Such data would help to redefine the formulation strategies for conventional and/or novel drug delivery systems and recommend altogether new dose regimens for the patients. A screening is also needed to know more details about the composition of beverages including various food drinks, social drinks which are consumed routinely[4]. The Indian population generally consumed food drinks, social drinks. The most common beverages consumed by Indian population include; Tea, Coffee, Buttermilk, Aerited, non- Aerited etc. These beverages are consumed on large scale and people are yet to be aware of the possible interaction of these beverages with commonly used drugs which are available as over the counter (OTC) product viz. such as analgesic, anti- inflammatory agent etc. This work aims to focus on major issues of altered release or absorption pattern of some drugs that can be improved by minimizing side effect.

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluids and permeability of the drug across gastrointestinal membrane. The rate of drug dissolution is greatly influenced by disintegration of the tablet[5]. The drug will dissolve at a slower rate from a non disintegrating tablet due to exposure of limited surface area to the fluid. Hence, *in vitro* disintegration test is an official test. It is most commonly studied in either water or

simulated gastric medium and occasionally in intestinal medium. In the pharmacopoeia, these media have been prescribed to perform this test with the aim to test batch-to-batch reproducibility of tablets. But if the drugs are ingested with different beverages, it will affect the bioavailability of drugs. In some category of drugs, patients are counseled to take medication with fluids other than water like in pain-relief medications; to be taken with milk to avoid gastric disturbances.[6,7]

In the study of disintegration of cataflam (Diclofenac tablets 50 mg, novartis) in different beverages it was found that there was a delayed disintegration in whole milk and low fat milk compared with that in water (19.82 ± 1.82 min and 21.69 ± 0.41 min, respectively, versus 12.06 ± 0.11 min) It has also been reported that the disintegration time of bristaflam (Aceclofenac tablets 100 mg, Mexico) in whole milk and fat-free milk was longer than in calcium-fortified orange juice, commercial iced coffee, and regular Coca-Cola which, in turn, was longer than in water. Delay of 25.16 min has been reported for DT of same tablet in whole milk as compared to in water. Similarity, the disintegration time of Ultram (Tramadol tablets 100 mg, Novartis) in 2% milk was approximately 7 min longer than that in water

Objective of this project was to investigate the DT of an immediate release pain relief tablet in beverages such as milk, butter milk, fruit juice, and regular soft drink in comparison to its DT in water chosen for study were 6% and 3.5% milk, regular Sprite (soft drink), AmulMasti (butter milk) and orange (fruit) juice. Milk and juice are the most commonly taken beverages in breakfast; milk is also consumed at bedtime in Indian families. AmulMasti (buttermilk) beverage of choice after lunch. Soft drink is also taken during the day time with snacks.

MATERIALS AND METHOD

Commercial Tablet Model Dosage Forms

Three IR pain-relief tablets were chosen as study products. Diclofenac 50mg tablets (cataflam by novartis Pharmaceuticals, total tablet weight 346.7 ± 3.8 mg, *n* = 3), Aceclofenac tablet 100mg (Bristaflam by mexico, total tablet weight 333.6 ± 2.9 mg, *n* = 3), Tramadol (Ultram by novartistotal tablet weight 341.5 ± 2.3 mg, *n* = 3) were purchased from Atul medicines V.V.Nagar.

Study Media

Whole milk, Low fat milk, Tropicana juice, iced coffee, coco cola, Butter milk (AmulMasti) were obtained from local stores.

Methods

Each of the three pain relief tablets under study were dropped into one basket tube of the USP disintegration apparatus and loaded into a one-litre, low-form glass beaker filled with 800 mL of deionized water, then lowered into a bath containing 8.5 L of water. The temperature of the bath was maintained at 37.0 ± 1.0°C throughout the entire test period. The apparatus was calibrated based on the guideline of *USP 31–NF 27* to ensure that the basket ascended and descended in an immersion fluid at 29–32 cycles per minute until the tablet was completely disintegrated and fragments fell out of the stainless steel mesh[8]. The disintegration time was then recorded. In addition to the use of deionized water, Whole milk, low fat milk, coco-cola, Tropicana orange juice, iced coffee and butter milk were chosen as immersion media to study the beverage effect on tablet.

Statistical Analysis

MS Excel was used to manage raw data. Using Sigma Plot Exact Graphs and Data Analysis, independent *t*-test and one-way ANOVA were performed. Population differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Diclofenac, Aceclofenac and Tramadol in different test media were studied and are depicted in Table 1. Most of them showed delayed disintegration in test beverages. The control used was distilled water [9].

The three drug candidates chosen for the study disintegrated fastest in the soft drink, which contains compressed carbon dioxide. It may be

suggested that this instant DT may be due to pressure exerted by carbon dioxide gas in sprite irrespective of the drug. Moreover in earlier studies it has been reported that wherever faster disintegration is required, ingredients are chosen which evolve carbon dioxide and break up the tablet[10]. In the experiment, carbon dioxide has some effect on the tablet extremity and thus leads to faster disintegration. Statistical results also indicated that disintegration of all three IR pain relief medications studied gave lower values in regular soft drink than the results obtained in water suggesting faster absorption from GI tract.

The duration required for Diclofenac to disintegrate in the soft drink was 1.8 ± 0.74 min (n=6) and in water was 5.4 ± 0.11 min (n=6). The most significant result was of Tramadol tablets which showed the disintegration as 2.6 ± 0.89 min (n=6) as compared to 23.6 ± 0.76 min (n=6) in water. It showed a huge difference of nearly 20 min.

AmulMasti is a popular buttermilk brand which is consumed by many during lunch. The disintegration in this beverage showed slightly higher DT than water. The results obtained for Diclofenac, Aceclofenac were 2.9 ± 0.72min (n=6) and3.8 ± 0.21min (n=6) for as compared to 5.4 ± 0.11 min (n=6), 2.1 ± 0.12 min (n=6) in water, respectively. In Tramadol tablets the results differed showing DT of 4.8 ± 0.91 min (n=6) in butter milk and as high as 23.6 ± 0.76 min (n=6) in water. Again a vast difference of nearly 19 min.

Juice chosen for this study was orange Juice by Tropicana, a well known brand for juices. As compared to regular soft drink and buttermilk, the DT in Calcium fortified orange juice was found to be higher than water with all the three medications. The results were as stated 8.9 ± 0.6 for Diclofenac, 7.1 ± 0.17 for Aceclofenac and 25.6 ± 0.11 for tramadol tablets. There was a large difference in duration compared to water.

In Iced coffee DT was found to be slightly lower as compare to whole milk and low fat milk in all three medications. For Aceclofenac, Diclofenac and Tramadol tablets were found to be 11.2 ± 0.1, 19.9 ± 0.11 and 21 ± 0.89 respectively.

Milk is one of the most preferred beverages co-administered with medicines. It is psychological of many patients that co-administration with milk will help reduce the adverse effects of the drugs associated with gastric distress. The disintegration was carried in whole milk and low fat containing milk. The DT results obtained in milk require consideration as all the three medications used showed delayed disintegration. Results showed that 23.5 ± 0.7 for Diclofenac, 15.5 ± 0.8 for Diclofenac and 35.1 ± 0.5 for Tramadol tablets in low fat milk From the depicted data in table 1 it shows that disintegration time is higher in all three tablets in low fat milk as compare to water. Similar as in whole milk Disintegration time for Aceclofenac, Diclofenac and Tramadol tablets were 50.2 ± 0.5, 69.1 ± 0.53 and 105 ± 0.96 respectively. It shows that wide difference should be shown as compare to disintegration time in water all three tablets. The significant delay found in disintegration of medication chosen for study may be due to the lipidic nature of milk and viscosity of milk.

Disintegrants, important excipients of tablet formulation, are always added to the tablet to induce breakup of the tablet when it comes in contact with aqueous fluid. It can be further noted that most of disintegrants are hydrophilic in nature suggesting a requirement of quick dispersion in the aqueous medium. So also the standard medium for carrying out DT is water at $37\pm2^{O}C$. It suggests that DT is preferably carried out to check the aqueous dispersion of the tablet. So, delay in DT in milk as media, may be attributed to the lipidic nature of milk. It was also observed that DT was delayed more in whole milk compared to low fat milk which further confirms the increase in the DT can further be related to the viscosity of milk.

CONCLUSION

This study examined the effect of different beverages on the disintegration of IR pain relief medications.

Table 1: Disintegration times of (A) Aceclofenac Tablets (B) Diclofenac Tablets (C) Tramadol Tablets

Media	**D.T (Min.) Aceclofenac Tablets**	**D.T (Min.) Diclofenac Tablets**	**D.T (Min.) Tramadol Tablets**
Whole milk	50.2±0.5	69.1±0.53	105±0.96
Low fat milk	15.5±0.8	23.5±0.7	35.1±0.5
Iced coffee	11.2±0.1	19.9±0.11	21±0.89
Tropicana orange juice	7.1±0.17	8.9±0.6	25.6±0.11
Coco cola	0.8±0.2	1.8±0.71	2.6±0.89
Butter milk (Amulmasti)	2.9±0.72	3.8±0.21	4.8±0.91
Water **(Control)**	2.1±0.12	5.4±0.11	23.6±0.76

The results obtained were compared to the DT obtained in water. The beverages considered were regular soft drink (Coco-cola), buttermilk (amulmasti), fruit juice (Orange), Iced coffee, Whole milk and low fat milk. The pain relieving medications were Aceclofenac, Diclofenac and Tramadol tablets. The results obtained indicated very quick disintegration of medications with regular coco cola was used as medium. The disintegration of drug under study was delayed in butter milk and a considerably prolonged DT was observed in guava juice which may be due to its high viscosity. Considerable delay was obtained in results of DT using 3.5% and 6.5% milk. This may be due to the high lipid content in milk. This observation is of particular importance as often patients are counselled to take medications, especially pain relief medications, with milk to decrease the potential for gastric irritation. Since an IR pain medication is designed have prompt onset of action, patients should be made aware of any factor that hinders drug molecule transport to the absorption site. The patients on these medications should be advised against consuming these drugs with milk until more information on the administration of drugs with beverages and food is available.

It is also suggested that instead of using only a straight beverage as disintegration medium, a hybrid medium containing 0.1N HCl and the test beverage is proposed. These will mimic an environment close to the one actually present in the stomach. Other factors like the type of food, the age and the physicochemical properties of the drug will affect the disintegration of tablet *in vivo*.

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