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Research Article

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Availability and Stability of Crushed Warfarin Tablet in Different Solvents

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Abstract Introduction: The vast majority (65 % to 70 %) of all medicines are solid oral dosage forms. Overall, the advantages of tablet stability problems are rare; however, one major point for adequate efficacy is often not considered: which is the ability to swallow them. Therefore, manipulation of tablets for patients with swallowing difficulties may lead to medications errors and potential changes in drugs efficacy.
Aim: To measure the availability and stability of crushed Warfarin tablet in different solutions and the impact of crushing practice.
Method: Warfarin tablets were crushed using mortar and pestle and analyzed by using British Pharmacopeia Spectrophotometric to measure the content, dissolution and stability of the tablets in water, orange juice and syrup at different time intervals.
Results: The content of Warfarin after 4, 24 and 48 hours was not decreased by more than 5% except in orange juice which decreased by 12% which revealed the stability of crushed tablet in these solvent. The release of Warfarin sodium was more in water than orange juice and syrup as it was 85.5% compared to 46% and 44% in orange juice and syrup respectively.
Conclusion: Prior to this study, no information was available regarding the stability of Warfarin tablets when crushed and dispersed in assorted oral delivery vehicles. Crushed tablets dissolved in water and syrup and kept in a refrigerator are stable for 24 hours. This study demonstrated that the ability to deliver the expected dose of Warfarin is negatively impacted by such practices and patients may face serious clinical problems. However, further study is needed to measure the efficacy of crushed Warfarin by following INR of patients taking Warfarin through NG-tube.

Keywords Warfarin tablets, Stability

Introduction

The World Health Organization (WHO) defined quality assurance as a wide-ranging concept covering all matters that individually or collectively influence the quality of a product.
A medicinal product is designed to possess certain desirable properties, when the product is administered by the specified route; the active constituent should achieve the required rate and extent of bioavailability. The product itself should be efficacious, safe, and acceptable to the patient and should be convenient in use and stable. The stability of a product relates to its resistance to the various chemical, physical, and microbiological reactions that may change the original properties of preparation and the effects of such changes on the fitness of the product for use as a medicine [1].

Solid dosage form

The vast majority (65 % to 70 %) of all medicines are solid oral dosage forms such as tablets and capsules of different sizes and shapes. Solid oral dosage forms prevail because their manufacturing process is less complex and cheaper than the development of most other pharmaceutical formulations. Moreover, stability problems are rare, a variety of non-toxic excipients is available, and masking of taste is accomplished more easily than for liquids or orodispersible tablets. In addition, tablets and capsules lack relevant drawbacks of liquids accurate dosing. However, given all these advantages of

tablets and capsules, they have one major concern; as the most important requirement for adequate efficacy of solid oral dosage forms is the ability to swallow them and delivered appropriately to the site of dissolution. [2]

Altering a licensed solid oral drug products

There is evidence that swallowing issues and dysphagia are an increasing problem of the aging population that is affecting oral medication administration. There is a variety of clinical expressions of swallowing dysfunction caused by aging, acute or chronic disease conditions, decline in physiological functions and adverse drug reactions. About one third of patients in long term care facilities experience serious difficulties with swallowing solid oral dosage forms (SODF). Manipulations of the solid oral drug products occur frequently in nursery homes by crushing tablet, opening capsule etc, leading to medication errors and potential changes in drug product performance. The alteration of the drug products is performed with the best intention of the care giver to help the patients but bears concerns about safety and lawfulness. Alternative SODF and drug delivery technologies should be considered in the development of new and generic products and their prescription to overcome medication administration problems in patients with swallowing difficulties of SODF [3].

The reasons for tablet crushing are numerous, however crushing tablets has repercussions on the licensed status of the medicine and how the medicine may affect the patient.

Dispersible tablets may not give an even solution so part dosing e.g. dissolving one tablet in 10 ml of water then giving 5 ml equating to half the dose is potentially inaccurate.

Changing the formulation of a medicine may alter its bioavailability, efficacy and/or side effect profile. When switching from a sustained-release to a standard-release form of a medicine, the dose frequency will need to be adjusted accordingly.

Certain types of drug should never be altered without advice from a pharmacist and/or the manufacturers as these changes impose on the pharmacokinetics and pharmacodynamics of the drug.

Altering a solid-dose formulation should be reserved as last-resort and practiced only after appropriate advice from a pharmacist; alternative formulations of the medication in question should be considered initially e.g. Transdermal, Injectable, Buccal, Rectal, Intranasal, and Sublingual.

The prescribers should consider the stability of the product once opened to the environment, whether the dose preparation could be accurately repeated to get the same dose, and the safety of the person preparing or administering the product. Alteration of a solid oral formulation should be considered under Control of Substances Hazardous to Health (COSHH) regulations since there may be an increased exposure to chemical components.

The variation in the amount of drug reaching the systemic circulation due to formulation change may have impact on efficacy and the potential side effects, particularly in drugs with a narrow therapeutic window like; Phenytoin , Digoxin , Carbamazepine , Sodium valproate , Theophylline, Lithium ,Warfarin , Citalopram [4]

Stability of crushing tablet

Crushing an oral solid dosage form may have a negative impact on the stability of the drug substance. If an enteric coating, which protects a drug from the acidic environment in the stomach, is removed by crushing the tablet, the in vivo drug degradation will increase, with fewer drugs available to produce the desired clinical effect. Coatings are also added to oral solid dosage forms to protect the drug from the effects of light. Nifedipine is an example of a drug that is highly light sensitive after tablets have been crushed [5].

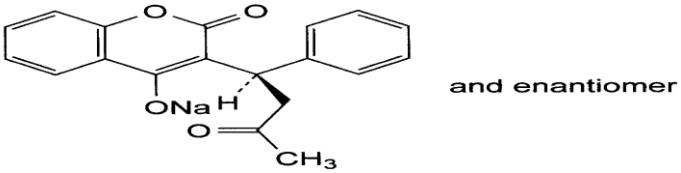
Quality testing techniques

Different techniques are used to identify the quality of pharmaceutical products.

These include spectrophotometry, chromatography techniques (liquid and gas), gravimetry, titrimetry, and radiochemistry. Different techniques possess varying degrees of selectivity, sensitivity, precision, accuracy, cost and speed.

The most common and widely used techniques are spectrophotometry and chromatography [6].

Warfarin tablet



Sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate

Molecular Formula: $C_{19}H_{15}NaO_4$

- Action and use :

Vitamin K epoxide reductase inhibitor; oral anticoagulant (coumarin)

Warfarin available as Warfarin Sodium and Warfarin Sodium Clathrate

- Preparations :

Warfarin tablets contain Warfarin Sodium or Warfarin Sodium Clathrate.
Warfarin tablets prepared from Warfarin Sodium are not necessarily interchangeable with Warfarin tablets prepared from Warfarin Sodium Clathrate [7].

Aim

- Evaluate the release of crushed warfarin tablet in different solvent
- Measuring the stability of crushed warfarin tablet in different solvent.

Materials and Methods

Equipment

- **Shimadzu spectrophotometer**

Model 1680-UV/ visible spectroscopy double beam with PC control and capability of derivative mode (Japan)
Chemicals: Warfarin Sodium Clathrate tablets 5mg; batch no. 543021218, 2 mg; batch no. 543021220, and 1mg; batch no. 543021230 and Warfarin working standard.
Solvents: Fresh orange juice, Distilled water and Syrup.

Method

Assay of warfarin tablets;
Twenty tablets from each warfarin concentration (5 mg, 2 mg and 1 mg) was accurately weighed and powdered using mortar and pestle, a quantity of powder equivalent to 1 mg warfarin was accurately weighed and transferred to 100 ml volumetric flask using distilled water, dissolved and the volume completed to 100 ml with water, filtered and the filtrate was measured using spectrophotometry at wavelength 307nm and 360nm, the concentration of warfarin in each table was calculated.

Stability Test

Orange juice, distilled water and syrup were used as solvent for studying the stability and content of warfarin crushed tablets.
Three warfarin tablets from each concentration (5 mg, 2 mg and 1 mg) was crushed separately using mortar and pestle, the powder of each tablet was transferred to test tubes; to tube one 2.7 ml orange juice was added , 2.7 ml distilled water was transferred to tube two and 2.7 ml syrup was transferred to tube three, the powdered was dissolved by shaking (These solution was kept in refrigerator to study their stability, from each tube 1 ml was accurately transferred to 25 ml volumetric flask and the volume was completed using distilled water and the solution was filtered using whatman filter paper; 2ml from the filtrate was transferred to 25 ml volumetric flasks and the volume was completed to 25 ml by distilled water. The absorbances of these solutions were measured using UV-Spectrophotometer at wave length 307 nm and 360 nm.
To study the stability of these preparation the absorbance was measured at different times interval; first after preparations, after 4 hr kept in room temperature and after 24 hr kept in the refrigerator for 5mg, 2 mg and 1 mg tablet, in addition the 2 mg table preparation was measured after 48 hr been kept in refrigerator.
The analysis was repeated three times and the average was calculated.

Dissolution Test

The availability of crushed warfarin tablet was studied using dissolution method.
Warfarin tablet was crushed and dissolved in the three solvent separately and transfer to one liter beaker and the volume was completed to 900 ml with water and maintained at a temperature of 37°C.
After 45 minutes, sample was withdrawn, and the absorbance was measured at the maxima at 307 nm and 360 nm, the content dissolved in the specified time was calculated [7].

Results and Discussion

Assay of warfarin

Table 1: The concentration of warfarin sodium in whole and crushed warfarin tablets in different solvent

Tablets in different solvent	1 mg (% Conc.±sd)	2 mg (% Conc.±sd)	5 mg (%Conc.±sd)
Whole warfarin tablets	100.2 ± 0.83	95.5 ±0.64	97.3 ±0.14
Crushed warfarin tablets in water	71.0 ±3.5	67.0 ± 2.1	74.5 ± 0.71
Crushed warafrin tablets in orange juice	71.0 ± 3. 5	59.0 ±1.15	66.5 ± 0.71
Crushed warafrin tablets in syrup	71.0 ± 1. 13	67.0 ± 1. 41	74.0 ± 2.8

The concentration of warfarin sodium in crushed tablets was significantly decreased by more than 20% from the initial concentration in all solvent.

Stability

The concentration of warfarin sodium in crushed warfarin tablet (5, 2, 1 mg) dispersed in various vehicles (water , orange juice, syrup), was calculated from declared absorbance at 4 hours in room temperature and after 24 and 48 hours in refrigerator. The results were shown in the tables below;

Results of warfarin tablet 1 mg

The results of stability and content of warfarin sodium in 1 mg crushed warfarin tablet in various vehicles (water, orange juice, syrup) at different time interval were shown in table (2).

Table 2: Comparison of stability of warfarin tablet 1 mg after crushing in different solvent

Time (hrs)	% Conc. in Water (w/v) ± sd	% Conc. in Orange juice (w/v) ± Sd	% Conc. in Syrup (w/v) ± Sd
zero	71 ± 3.5	71 ± 3. 5	71 ± 1. 13
4	69 ±1.6	68 ± 2.12	69 ± 1.27
24	67± 4.6	67 ± 1.13	68 ± 1.34
t-test		-10.9*	-1.9*

*Calculated t-values for water with orange juice and syrup is less than *Tabulated t- value = 4.3(at 95% confidence)*

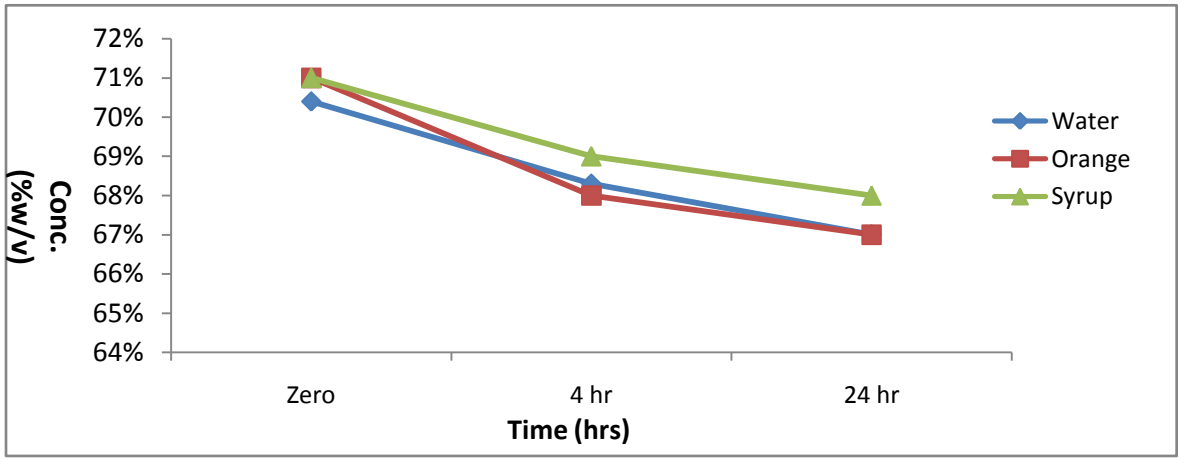


Figure 1: Stability of warfarin 1 mg crushed tablet in different solvent

Results of warfarin tablet 2 mg

Table 3: Comparison of stability of warfarin tablet 2 mg after crushing in different solvent

Time (hrs)	% Conc. in Water w/v) ± Sd	% Conc. in Orange juice (w/v) ± Sd	% Conc. in Syrup (w/v) ±Sd
zero	67.0 ± 2.1	59 ±1.15	67.0 ± 1. 41
4	67.0 ±2.8	56 ± 0.57	64.0 ± 2.8
24	66.0 ± 3.9	56 ± 1.85	64.0 ± 0.71
48	64.0 ± 3.8	52* ±1.9	64.0 ± 5.29
t-test		**12.0****	**1.67****

*More than 5% degradation

**Calculated 2- tailed t-values for water with orang juice and syrup = 12.0 and1.67 respectively; *(Siginficant 0.001 and 0.194 respectively at 95%confidence)*

The water taken as standard as it is neutral compare to orange juice (pH 4.4) and liquid to comare to syrup solvent; from 2 tailed t-test results; it is clear that there is no significant differences in stability of warfarin sodium in the three solvent for dissolving crushed warfarin tablet.

The warfarin sodium dissolved in orange juice is unstable after 24 hour as the results after 48 hour show about 12% loss in content of warfarin sodium.

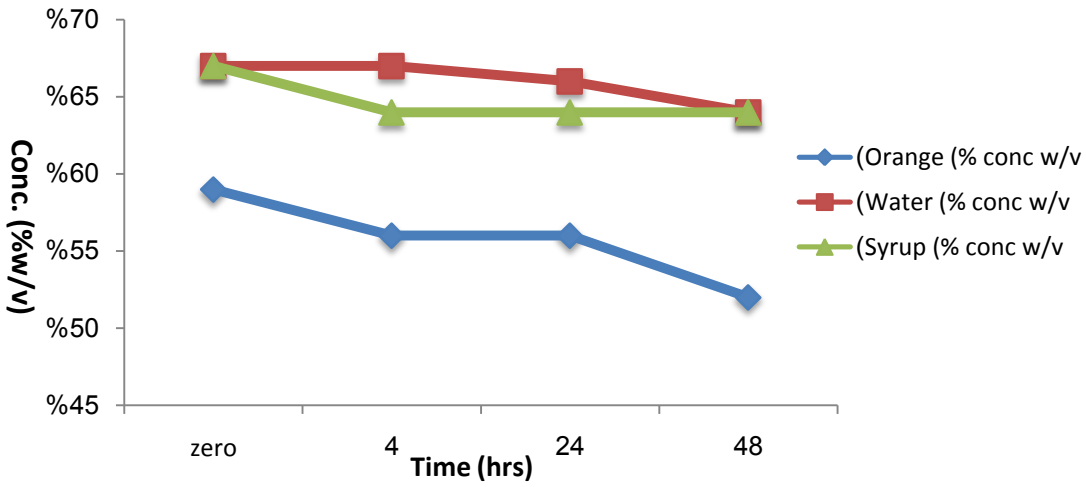


Figure 2: Stability of warfarin tablet 2 mg after crushing in different solvent

Dissolution

The percentage release of warfarin sodium from crushed warfarin tablet dissolved in different solvent was studied and the results shown in table (4)

Table 4: Percentage release of warfarin 5 mg crushed tablet in different solvent

Solvent	Release %
Water	85.8
Orange	46.3
Syrup	44.2

The British pharmacopeia acceptance criteria for dissolution of immediate release formulation are Q+ 5 which is equal to 80%.

The results obtained show that warfarin sodium is better released from water than orange juice and syrup.

Discussion

In this research we study the content, stability and in vitro release of warfarin tablet when crushed and mixed with syrup, water and orange juice for administration to patient facing problem of swallowing.

The content of warfarin sodium in the three solvent is revealed by the analysis at zero time and compare with analysis of whole tablets; which for 1 mg is 71.0% in all solvents compare to 100.2% for whole tablets and for 2 mg is 67% in water and syrup and 59% in orange juice compare to 95.5% for whole tablets while the zero results for 5 mg is about 74% in water and syrup and 70% in orange juice; compare to 97.3% for whole tablets, these results reflect that the content of warfarin sodium in water and syrup solvent almost same while the content is less in orange juice inspite of that all results in the three solvent is less than the results of whole tablets by more than 20% and less than the required standard of British and United State pharmacopeia which state that the content of warfarin sodium in tablet should not be less than 95 % [7& 8]. This low content in crushed tablet may be due to loss during process of crushing and transefer or due to the solvent used not release warfarin sodium from tablet.

The medications when crushed and mixed with common food vehicles or thickening agents may be influenced by the properties (e.g. viscosity) and structure of the carrier. This may be critical for certain medications with a narrow therapeutic index or when immediate release is required for fast therapeutic action. These findings bring into question the potential clinical implications of the addition of these agents to medications for the purpose of dose delivery and indicate that further investigation of thickened fluids and their potential to influence therapeutic outcomes is warranted [9].

These influence of solvent on release of warfarin sodium from tablet was in agree with study done by *Manrique-Torres, et al.* as they found that thick food products such as honey, jam and yoghurt, which are also used to aid delivery of crushed medications for people who cannot or do not like to swallow whole tablets and capsules, had a relatively small and drug-dependent impact on dissolution. In particular, jam, yoghurt and honey slowed dissolution

for crushed carbamazepine and warfarin, this actually served to create a release profile that was more like that of the whole tablet than the crushed tablet, which reinforces the fact that each dosage form has the potential to respond differently to crushing and mixing with vehicles. [9]

The low content obtained (59%, 67%, 70%...etc) from crushing tablet relveal the practice done in hospital and home as the loss be due to malpractice in powdering and transfer of crushed tablet to the patient; as a study designed by Mercovich, et.al., to observe the extent of solid dosage form modification in current practice and explore how information access and quality for nursing staff is contributing to rates of inappropriate dosage form modification and safety of patient. The equipment used to crush medications either a mortar and pestle or a specifically designed pill crushing device. In all instances, this equipment was shared among residents and was not cleaned between different residents. Medication spillage or loss was observed in all incidences of administration where drug powder was spilled from the vessel onto the medication trolley or floor; or medication loss occurred through incomplete administration of the vehicle containing the crushed medications to the resident. Residual vehicle containing the drug was observed to remain in the containing vessel following all (100%) administrations and was discarded. The observed 32% incidence of inappropriate dosage form modification was almost double that reported in a similar study, which recorded 17% of inappropriate crushing. Although there is no pharmacodynamic contraindication to crushing some of the tablets observed, such as amiodarone and warfarin, there is a high risk of incomplete or variable dosing from crushing these medications, which may result in clinically significant adverse outcomes for the resident [10].

The incidence of inappropriate crushing is much high to occurs with patient that crush his medication at home. This will have impact on patient taking the warfarin tablet as his receive subdose which will contribute in the therapeutic effect of warfarin.

On the another hand , prior to this study, no information had been available regarding the stability of warfarin tablets when crushed and dispersed in assorted oral delivery vehicles, including water, orange juice, and syrup . As shown in tables 4 and 8 the warfarin sodium is inspite of low release and content of crushed tablet their stablility not affected for 24 hour in all solvent as the content not reduced by more than 5% as mentioned by definition of stability by World Health Organization; also show stability for 48 hour in water and syrup while show instability in orange juices in 48 hrs as the content is decreased by12%, [1].

The results show no significant different in the stabilty in orange juice and syrup compare to water as revealed by one paired sample t-test. The statistical analysis for results of 2 mg obtained as follow t-test; -12.0 and -1.67 compare to *Tabulated t- value =3.18 (at 95%confidence)* and Sd.;1.7 and 1.5 being less than 2 and SEM; 0.85 and 0.75 less than one in orange juice and syrup respectively; and the statistical analysis for results of 1 mg tablets as follow t-test; -10.9 and -1.9 compare to *Tabulated t- value =4.3 (at 95%confidence)* and Sd.;1.5 and 1.5 being less than 2 and SEM; 0.88 and 0.88less than one for orange juice and syrup respectively; which reveal that no significant difference in stability of warfarin sodium between orange juice.

The result obtained from this study show that dissolution rate and drug released of crushed warfarin tablet in water is 85.5 % compare to 46.5% and 44.2% in orange juice and syrup respectively, this is due to the pH of orange juice can be the factor for low release rate. However, the lower dissolution rate in syrup may due to the viscosity of syrup. The better dissolution of crushed tablet in water revealed the results obtained by Manrique-Torres, et al as the crushing the tablet and delivering with water resulted in faster dissolution, with warfarin tablet reaching 85% dissolution within 20 minute. In addition, alterations in bioavailability such as this are of particular concern for drugs that have a narrow therapeutic index (such as, warfarin) because the concentration absorbed into the blood stream may not reach that required to elicit the therapeutic effect, [9].

Warfarin has been classified as class I according to Biopharmaceutical Classification Scheme (BCS) when used as the sodium salt and tested in water and, BCS II when used as the free acid slow dissolution from the whole warfarin sodium tablet tested in simulated gastric fluid (causing the warfarin to become unionized and therefore less soluble). BCS II classification is most appropriate for the conditions orange juice dissolution results as been 46.5% which is also in agree study done by [9].

Measuring bioavailability by obtain International Normalized Ratio (INR), INR measurement has a critical role in maintaining the warfarin response within a therapeutic range, to provide the benefits of anticoagulation, while avoiding the risks of hemorrhage so crushing of tablet and dissolving in solvent with poor solubility and consequently availability of warfarin may affect the INR measurement as proof by the study done by Salem D, et al. diet and alcohol change INR in stable patient, [11].

However, take warfarin as crushed tablet by feeding tube, not taken seriously as a factor that affecting INR level, which know that crushed narrow therapeutic index drugs can alterations in bioavailability. Were the Institute for

Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Conclusion

It is a common practice to crush solid oral formulations, such as tablets, and disperse them in various vehicles to facilitate administration, including NG tube administration in water, to patients who have difficulty swallowing. This study has demonstrated that the ability to deliver the expected dose of warfarin is negatively impacted by such practices and patient may face serious clinical condition in addition this practice may affect the nurse and other health care provider if the drug is hazardous in addition may affect the safety of patient due to trace of different medicinal products being handled by same procedure due to contamination and cross contamination of medicinal products problem.

Inspite of these the study reveal that warfarin sodium crushed and dissolved in water, orange juice and syrup is stable for 24 hours being kept in a refrigerator.

Reference

1. World Health Organization (2007), quality assurance of pharmaceutical products, volume
2. Schiele, Julia T., et al. (2013) "Difficulties swallowing solid oral dosage forms in a general practice population: prevalence causes, and relationship to dosage forms." European journal of clinical pharmacology 69.4: 937-948.
3. Stegemann, S., M. Gosch, and J. Breitkreutz. (2012) "Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy." International journal of pharmaceutics 430.1: 197-206.
4. GUIDELINES FOR BREAKING OR CRUSHING TABLETS. (2012). 1st ed. [PDF] NHS. Availableat:http://www.humber.nhs.uk/Downloads/Services/Pharmacy/Guidelines/Breaking%20or%20crushing%20tablets.pdf [Accessed 14 Mar. 2015].
5. Verrue C, et al. (2010) Tablet-splitting: a common yet not so innocent practice. Journal of Advanced Nursing (2010); 67: 26-32.
6. Beckett A. H. and Stenlake J. B. (2001) Quantitative and qualitative method of analysis. Practical Pharmaceutical Chemistry, 4th edition, 296-300.
7. British Pharmacopeia (BP) (2013) spectrophotometric method for dissolution of warfarin tablets,.
8. United State Pharmacopeia USP, monograph of warfarin tablets, (2014).
9. Manrique-Torres, Yady Juliana, et al. (2014) "Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release?" Journal of Pharmacy & Pharmaceutical Sciences 17.2: 207-219.
10. Mercovich, Nicole, Greg J. Kyle, and Mark Naunton. (2014)"Safe to crush? A pilot study into solid dosage form modification in aged care." Australasian journal on ageing 33.3: 180-184.
11. Salem D, O'Gara P, Madias C, Pauker S.(2008) Valvular and structural heart disease: American College of Chest Physicians evidence-based clinical practice guidelines (8thed). Chest; 133:593S-629S.