Abstract:

The present disclosure relates to a novel dissolution medium for analyzing the effect of alcohol on drug release and permeation pattern. The dissolution medium contains alcohol containing fluid and water. The amount of alcohol containing fluid in the dissolution medium of the present disclosure is optimized so as to maintain 2.6 wt% of absolute alcohol. The present disclosure also relates to a process for analyzing the effect of co-administration of alcohol or alcoholic beverages on the release and permeation profile of a drug.

We claim

1. A novel dissolution medium for analyzing the effect of alcohol on drug release and permeation pattern, said medium comprising:

    a. at least one alcohol containing fluid; and

    b. water,

    said medium characterized in that the concentration of absolute alcohol in said medium is 2.6 wt%.

2. The medium as claimed in claim 1, wherein the alcohol containing fluid is at least one alcoholic beverage selected from the group consisting of beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura, sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The use of the expression "at least" or "at least one" suggests the use of one or more elements or ingredients or quantities, as the use may be in the embodiment of the invention to achieve one or more of the desired objects or results.

The numerical values given for various physical parameters, dimensions and quantities are only approximate values and it is envisaged that the values higher than the numerical value assigned to the physical parameters, dimensions and quantities fall within the scope of the invention and the claims unless there is a statement in the specification to the contrary.

While certain embodiments of the inventions have been described, these embodiments have been presented by way of example only, and are not intended to limit the scope of the inventions. Variations or modifications in the process or compound or formulation or combination of this invention, within the scope of the invention, may occur to those skilled in the art upon reviewing the disclosure herein. Such variations or modifications are well within the spirit of this invention. The accompanying claims and their equivalents are intended to cover such forms or modifications as would fall within the scope and spirit of the invention.

3. The medium as claimed in claim 1, wherein the alcohol containing fluid is at least one medicated alcoholic preparations selected from the group consisting of syrups, asava, and arishta.

4. A process for analyzing the effect of alcohol on drug release and permeation pattern, said process comprising the following steps:

a. preparing a dissolution medium comprising at least one alcohol containing fluid and water, said medium characterized in that the concentration of absolute alcohol in said medium is 2.6 wt%;

b. pouring said dissolution medium into a first compartment of a dissolution apparatus,

   i. said first compartment further comprises at least one everted sac of goat ileum, at least one aerator tube and a shaft; and

   ii. wherein the everted sac of goat ileum of said first compartment comprises water,

c. pouring water into a second compartment of said dissolution apparatus;

   i. said second compartment further comprises at least one everted sac of goat ileum, at least one aerator tube and a shaft; and

   ii. wherein the everted sac of goat ileum of said second compartment comprises water;

d. admixing at least one theoretical dose of at least one dosage form into said first compartment and said second compartment;

e. rotating said shafts of said first compartment and said second compartment at a speed ranging between 50 and 100 rpm;

f. collecting a predetermined amount of samples from said first compartment, second compartment, everted sac of said first compartment and the everted sac of said second compartment, at a predetermined period of time; and

g. subjecting the samples for analysis to obtain the effect of alcohol on drug release and permeation pattern.

5. The process as claimed in claim 4, wherein the method step (f) further comprises

i. selectively replacing said amount of samples into said first compartment using the dissolution medium as claimed in claim 1;

ii. selectively replacing said amount of samples into said second compartment, and the everted sac of said first compartment and the everted sac of said second compartment using water; and

iii. iterating the method steps (f) and (g) for a predetermine period of time to study the effect of alcohol on drug release and permeation pattern.

6. The process as claimed in claim 4, wherein the alcohol containing fluid is at least one alcoholic beverage selected from the group consisting of beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura, sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon

whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

7. The process as claimed in claim 4, wherein the alcohol containing fluid is at least one medicated alcoholic preparations selected from the group consisting syrup, asava, and arishta.

8. The process as claimed in claim 4, wherein the dosage form is in at least one form selected from the group consisting of tablet, capsule, emulsion, suspension, syrup, gel, cake, powder and semisolid.

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FIELD OF DISCLOSURE:

The present disclosure relates to a novel dissolution medium. The present disclosure also relates to a process for analyzing the effect of alcohol on drug release and permeation pattern using the novel dissolution medium.

BACKGROUND:

Consumption of alcoholic beverages has become an indispensable part of modern life style and also carries social status in many communities. In addition to this, consumption of medicines with alcoholic beverage has also become part of routine life. It is observed that alcohol potentially influences the absorption, metabolism and excretion of active ingredient or drug present in the medicines, which subsequently, leads to dose dumping and related side effects.

Further, modified release (MR) oral formulations which are intended for once or twice daily administration and are designed with a higher unit dose of the drug than conventional formulations, exhibits rapid release of the drug, or dose dumping when co-administered with alcoholic beverages. Abovementioned problems eventually, affect safety and efficacy of the drug.

Accordingly, in 2005, the FDA published an alert for healthcare professionals regarding the impending effects of alcoholic beverages on drug release. In this report, FDA mentioned that alcohol increases peak plasma concentration of drug, which eventually, causes lethal dose dumping. Several other publications have also outlined the influence of alcoholic beverages on the release pattern of several oral dosage forms.

For instance, Fadda et al. disclosed that, the oral dosage forms having higher solubility in hydro-alcoholic solutions exhibits rapid drug dissolution and release in the presence of ingested ethanol.

Therefore, with the increase in the risk of co-consumption of alcoholic beverages and medicines, there is a need fora formulation of a drug that exhibits robust release of a drug in the presence of ingested alcohol. However, to arrive at a drug formulation that releases drug in a pre-determine fashion even in the presence of alcohol there is a need for a dissolution medium. Further, there is also a need for a process for analyzing the effect of alcohol on drug release and permeation pattern. Accordingly, the present invention provides the dissolution medium and a process for analyzing the effect of alcohol on drug release.

OBJECTS:

Some of the objects of the present disclosure, which at least one embodiment herein satisfies, are as follows:

It is an object of the present disclosure to ameliorate one or more problems of the prior art or to at least provide a useful alternative.

It is another object of the present disclosure to provide a novel hydro-alcoholic dissolution medium.

It is still another object of the present disclosure to provide novel hydro-alcoholic dissolution medium for analyzing the effect of alcohol on drug release and permeation pattern.

It is yet another object of the present disclosure to provide novel hydro-alcoholic dissolution medium for analyzing the robustness of the dosage forms when co-administered with alcohol or alcohol containing fluids.

It is a further object of the present disclosure to provide a novel process for analyzing the effect of alcohol on drug release and permeation pattern.

It is still further object of the present disclosure to provide a process for analyzing the robustness of the dosage forms when co-administered with alcohol or alcohol containing fluids.

Other objects and advantages of the present disclosure will be more apparent from the following description which is not intended to limit the scope of the present disclosure.

DETAILED DESCRIPTION OF ACCOMPANYING DRAWINGS:

Figure 1: illustrates calibration curve of Metformin hydrochloride in water;

Figure 2: illustrates calibration curve of Diclofenac sodium in purified water;

Figure 3: illustrates percentage release of Metformin HCl from Met IR tablets in water;

Figure 4: illustrates percentage release of Metformin HCl from Met SR tablets in water;

Figure 5: illustrates percentage release of Diclofenac Na from Diclo DR tablets in water;

Figure 6: illustrates percentage release of Diclofenac Na from Diclo SR tablets in water;

Figure 7: illustrates release profile of Metformin HCl from Met IR tablets in different hydroalcoholic media and water;

Figure 8: illustrates release profile of Diclofenac Na from Diclo DR tablets in different hydroalcoholic media and water;

Figure 9: illustrates release profile of Metformin HCL from Met SR tablets in different hydroalcoholic media and water;

Figure 10: illustrates release profile of Diclofenac Na from Diclo SR tablets in different hydroalcoholic media and water;

Figure 11: illustrates release profile of Metformin HCl from Met IR tablets in white wine , red wine and water;

Figure 12: illustrates release profile of Metformin HCl from Met SR tablets in white wine, red wine and water;

Figure 13: illustrates release profile of Diclofenac Na from Diclofenac DR tablets in white

wine, red wine and water;

Figure 14: illustrates release profile of Diclofenac Na from Diclofenac SR tablets in white wine, red wine and water;

Figure 15: illustrates permeation of Metformin HCl from Met IR tablets in different hydroalcoholic media and water;

Figure 16: illustrates permeation of Metformin HCl from Met SR tablets in different hydroalcoholic media and water;

Figure 17: illustrates permeation of Diclofenac Na from Diclo DR tablets in different hydroalcoholic media and water; and

Figure 18: illustrates permeation of of Diclofenac Na from Diclo SR tablets in different hydroalcoholic media and water;

SUMMARY:

In accordance with one aspect of the present disclosure there is provided a novel dissolution medium for analyzing the effect of alcohol on drug release and permeation pattern, said medium comprising:

a. at least one alcohol containing fluid; and

b. water,

said medium characterized in that the concentration of absolute alcohol in said medium is 2.6 wt%.

Typically, the alcohol containing fluid is at least one alcoholic beverage selected from the group consisting of beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura,

sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey; manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

Typically, the alcohol containing fluid is at least one medicated alcoholic preparations selected from the group consisting of syrups, asava, and arishta.

In accordance with another aspect of the present disclosure there is provided a process for analyzing the effect of alcohol on drug release and permeation pattern, said process comprising the following steps:

a. preparing a dissolution medium comprising at least one alcohol containing fluid and water, said medium characterized in that the concentration of absolute alcohol in said medium is 2.6 wt%;

b. pouring said dissolution medium into a first compartment of a dissolution apparatus,

   i. said first compartment further comprises at least one everted sac of goat ileum, at least one aerator tube and a shaft; and

   ii. wherein the everted sac of goat ileum of said first compartment comprises water,

c. pouring water into a second compartment of said dissolution apparatus;

   i. said second compartment further comprises at least one everted sac of goat ileum, at least one aerator tube and a shaft; and

ii. wherein the everted sac of goat ileum of said second compartment comprises water;

d. admixing at least one theoretical dose of at least one dosage form into said first compartment and said second compartment;

e. rotating said shafts of said first compartment and said second compartment at a speed ranging between 50 and 100 rpm;

f. collecting a predetermined amount of samples from said first compartment, second compartment, everted sac of said first compartment and the everted sac of said second compartment, at a predetermined period of time; and

g. subjecting the samples for analysis to obtain the effect of alcohol on drug release and permeation pattern.

The method step (f) of the present disclosure further comprises the following steps:

i. selectively replacing said amount of samples into said first compartment using the dissolution medium of the present disclosure;

ii. selectively replacing said amount of samples into said second compartment, and the everted sac of said first compartment and the everted sac of said second compartment using water; and

iii. iterating the method steps (f) and (g) for a predetermine period of time to study the effect of alcohol on drug release and permeation pattern.

Typically, the alcohol containing fluid is at least one alcoholic beverage selected from the group consisting of beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter. stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura,

sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

Typically, the alcohol containing fluid is at least one medicated alcoholic preparations selected from the group consisting syrup, asava, and arishta.

Typically, the dosage form is in at least one form selected from the group consisting of tablet, capsule, emulsion, suspension, syrup, gel, cake, powder and semisolid.

DESCRIPTION:

Alcohol consumption has been a part of individual's lives since ancient times. Consumption of alcohol has shot up in the past decade as a result of lavish and Gen next lifestyle changes. Other aspects associated with lifestyle or longevity includes diseases and disorders like diabetes and hypertension. A jet- setting life and consequent indiscriminate use of drugs has lead to constant consumption of pain killers. Due to lifestyle diseases and habit of consuming alcohol, drugs are being more often co-consumed with alcohol.

It is observed that co-consumption of alcohol or alcoholic beverages along with medicines potentially influences the release and the permeation profile of the active ingredient or drug present in the medicines, which subsequently, leads to dose dumping and related side effects of said drugs. The dose dumping or side effects may be lethal to a person co-consuming the alcohol with medicine.

Usually, *in-vitro* dissolution testing is used for analyzing release profile of the drug. Further, some of the prior art discloses *ex-vivo* methods for analyzing permeation profile of the drug. However, none of the prior art discloses the dissolution medium for analyzing the effect of co-consumption of alcohol or alcoholic beverages on the release and permeation profile of the active ingredient or drug present in the medicines.

Therefore, with the aim of analyzing the effect of co-administration of alcohol or alcoholic beverages on the release and permeation profile of a drug and arrive at formulation of a drug that exhibits robust release of a drug in the presence of ingested alcohol, the inventors of the present disclosure have extensively studied the content of absolute alcohol in the known alcoholic beverages. The inventors have developed a dissolution medium containing aforementioned amount of alcoholic beverages and a dissolution medium containing 24ml of absolute alcohol. The inventors surprisingly found that the release and permeation profile of the drug in the dissolution medium containing alcoholic beverages is equivalent to that of the dissolution medium containing 24ml of absolute alcohol.

Accordingly, the present disclosure provides a novel dissolution medium for analyzing the effect of alcohol on drug release and permeation pattern. The dissolution medium comprises alcohol containing fluid and water. The amount of alcohol containing fluid in the dissolution medium of the present disclosure is optimized so as to maintain 2.6 wt% of absolute alcohol.

The alcohol containing fluid used for preparing the dissolution medium of the present disclosure includes but is not limited to beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura, sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling

wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, tuica, vodka, bourbon whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

Typically, the alcohol containing fluid includes medicated alcoholic preparations such as syrups, asava, arishta, combinations thereof and the like.

In accordance with another aspect of the present disclosure there is also provided a process for analyzing the effect of alcohol on drug release and permeation pattern. The process includes the following steps:

In the first step, a dissolution medium is prepared using one or more alcohol containing fluids and water. The amount of alcohol containing fluid in the dissolution medium of the present disclosure is optimized so as to maintain 2.6 wt% of absolute alcohol.

In the second step, the dissolution medium is poured into a first compartment of a dissolution apparatus having at least one everted sac of goat ileum, at least one aerator tube and a shaft.

In the third step, the water is poured into a second compartment of a dissolution apparatus having at least one everted sac of goat ileum, at least one aerator tube and a shaft.

The everted sac of goat ileum of the first and the second compartment is filled with water.

In the fourth step, a theoretical dose of at least one dosage form is admixed into the first compartment and the second compartment;

In the fifth step, the shafts of the first compartment and the second compartment are rotated at a speed ranging between 50 and 100 rpm.

In the sixth step, a predetermined amount of samples are collected at a predetermined period of time from the first compartment, second compartment, everted sac of the first compartment and the everted sac of the second compartment.

The amount of sample collected from the first compartment, is then replaced using the dissolution medium of the disclosure. The amount of samples collected from the second compartment, everted sac of the first compartment and second compartment is replaced uing water.

In the seventh step, the samples are analyzed to obtain the effect of alcohol on drug release and permeation pattern.

In accordance with one embodiment of the present disclosure the sixth and seventh steps are iterated to obtain the effect of alcohol on drug release and permeation pattern.

The alcohol containing fluid used in the process of the present dislocure includes one or more alcoholic beverage such as beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura, sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine, liqueurs and combinations thereof.

Non limiting examples of the medicated alcoholic preparations used as alcohol containing fluid includes asava, arishta and combinations thereof

Typically, the dosage form includes tablet, capsule, emulsion, suspension, syrup, gel, cake, semisolid, and powder.

The present disclosure will now be discussed in the light of the following non-limiting examples:

Examples:

Example 1: Drug **Release Studies in water and the dissolution mediums (hydro-alcoholic medium) of the present disclosure:**

Step I: Construction of Calibration Curve

a. **Metformin HCl**

UV-Visible Spectroscopy: Accurately weighed 10 mg of the drug was dissolved in Distilled Water in 100 ml volumetric flasks to obtain a stock solution of 100µg/ml. The solution was further diluted to obtain solution of 10 µg/ml concentration. Appropriate dilutions were made to obtain the standard solutions in the concentration range of 1-10 µg/ml. The maximum absorption (λ_{max}) were noted by using UV/VIS spectrophotometer- JASCO – V530) in the range of 200-800 nm for drug solution. The absorbance of the each of the standard solution was recorded at λ_{max} of 233nm and illustrated in figure 1. The straight line graph in figure 1 has r^2 0.9954 which indicates that Metformin hydrochloride obeys the Beer Lambert's law in the range of 1 -6 µg/ml.

b. **Diclofenac Sodium**

UV-Visible Spectroscopy:

Accurately weighed 10 mg of the drug was dissolved in Distilled Water in 10 ml volumetric flasks to obtain a stock solution of 1000 µg/ml. The solution was further diluted to obtain solution of 100 µg/ml concentration. The max Appropriate dilutions were made to obtain the standard solutions in the concentration range of 5 to 30 µg/ml. Maximum absorption (λ_{max}) were noted by using UV/VIS spectrophotometer- JASCO – V530) in the range of 200-800 nm for drug solution. The absorbance of the each of the standard solution was recorded at λ_{max} of 277nm and illustrated in figure 2. The straight line graph in figure 2 has r^2 0.9988 which indicates that Diclofenac sodium obeys the Beer Lambert's law in the range of 5-30µg/ml.

The various brands of Metformin HCl tablets, IR as well as SR used were coded as follows:

Step II: Preparation of dissolution medium (hydroalcoholic medium) of the present disclosure containing 2.6 wt% of absolute alcohol:

Commercially available cans or bottles of beer serve 300ml of the beverage and that is the minimum quantity of beer usually consumed at any single point. Hence, medium containing beer was prepared by diluting 300 ml of beer (strong beer 8% v/v ,mild beer 5% v/v) with sufficient quantity of purified water to make 900 ml. Similarly, one peg of rum (40% v/v) represents 60 ml . Hence, this medium was prepared by diluting 60 ml of rum with sufficient quantity of purified water to make the final volume. Moreover, a separate dissolution medium comprising of 40% v/v alcohol representing commercially available spirits (rum, whisky, vodaka etc) was used. The volume of the same was 60 ml diluted in similar manner as described for rum. Drug release/dissolution studies were carried out in medium containing strong beer, mild beer, 40% alcohol and rum for Met IR, Met SR, Diclo DR and Diclo SR formulations.

The various hydroalcoholic media were abbreviated as follows:

1. 300 ml mild kingfisher beer + 600 ml distilled water – Mild Beer
2. 300 ml strong kingfisher beer + 600 ml distilled water – Strong Beer
3. 60 ml rum+ 840 ml distilled water - Rum
4. 60 ml 40% alcohol + 840 ml purified water – 40% Alcohol
5. 60 ml red wine + 840 ml purified water – Red Wine
6. 60 ml white wine + 840 ml purified water – White Wine
7. 24ml absolute alcohol +876 ml purified water- dissolution mediums (hydroalcoholic medium)of the present disclosure

Step III: Release profile of Metformin HCl from Met IR Tablets and Met SR Tablets and release profile of Diclofenac Na from Diclo DR Tablets and Diclofenac SR tablets were studied using the dissolution mediums (hydro-alcoholic medium) of the present disclosure and the purified water.

1) **Metformin HCl** Immediate Release Tablets (Met IR)

Six tablets from within the same batch of each product were tested. The volume of dissolution media was 900 ml water maintained at 37±0.5 ^{0}C and a basket speed of 100 rpm was employed. The amount of Metformin HCl released from the Met IR was determined using UV – Visible Spectrophotometer (JASCO MAKE) at 233 nm wavelength. The data obtained were analyzed using PCP-DISSO software.

The effect of the dissolution mediums (hydro-alcoholic medium) of the present disclosure on the release profile of the Met IR was analyzed using the aforementioned procedure and replacing purified water with the hydro-alcoholic medium.

2) **Metformin HCl Sustained Release Tablets (Met SR)**

Drug release profile of Met SR in the water was studied by replacing the Met IR with Met SR in the procedure illustrated for analyzing the Drug release profile of Met SR in the water.

The effect of the dissolution mediums (hydro-alcoholic medium) of the present disclosure was analyzed using the aforementioned procedure and replacing purified water with the hydro-alcoholic medium of the present disclosure.

3) Diclofenac Sodium Delayed Release Tablets (Diclo DR)

Six tablets from within the same batch of each product were tested. The volume of dissolution media was 900 ml distilled water maintained at 37±0.5 ^{0}C and a paddle speed of 50 rpm was employed. The amount of Diclofenac released from the dosage form was determined using UV – Visible Spectrophotometer (JASCO MAKE) at 277 nm wavelength.

The effect of the dissolution mediums (hydro-alcoholic medium) of the present disclosure was analyzed using the aforementioned procedure and replacing purified water with the hydro-alcoholic medium of the present disclosure.

4) Diclofenac Sodium sustained Release Tablets (Diclo SR)

Drug release profile of Diclo SR in the water was studied by replacing the Diclo DR with Diclo SR Tablets in the procedure illustrated for analyzing the Drug release profile of Diclo DR in the water.

The effect of the dissolution mediums (hydro-alcoholic medium) of the present disclosure was analyzed using the aforementioned procedure and replacing purified water with the hydro-alcoholic medium of the present disclosure.

In vitro release of Metformin hydrochloride from Met IR in water indicates more than 80% drug release within fifteen minutes (Fig. 3), a release pattern of typical immediate release formulation. Similarly, the *In vitro* release of Metformin hydrochloride from Met SR in the water indicates release of 97% drug over a period of twelve hours (Fig. 4).

For Met IR tablets, it was found that the release of drug depends on the volume of alcoholic beverages. In rank order, it was observed that the drug release was faster in dissolution medium of the present disclosure containing strong beer followed by mild beer followed by

rum and 40 % alcohol. The release of Metformin hydrochloride was slowest in water in spite of high solubility of drug in water (Fig.3 and Fig. 7). The release rate of drug was affected by both the strength of alcoholic beverages as well as its volume. It should be noted that beer is a fermentation product while rum is a distillation product. Various natural ingredients such as hops, malt etc are used in the manufacturing of the beer imparting it the typical flavor. Also, beer has property of reducing the surface as well as the interfacial tension evident from its foam forming tendency. All these contribute to the enhancement of solubility and in turn dissolution of the drug as demonstrated in figure 7

For SR formulations, the release of Metformin hydrochloride exhibited almost identical profile in 40 % alcohol and rum (Fig.9). However the release was retarded in the media containing strong and mild beer and was found to be least in water .Thus the strength rather than the volume of alcohol in the dissolution medium has profound effect on the drug release. This effect is attributed to the ability of alcohol to disrupt the sustained release mechanism. The same is reflected by model fitting (as depicted in table 1) where the best fit is shifted from matrix behavior to Peppas and first order. The lower 'n' value indicates analog transport which may be due to rapid dissolution of drug or relaxation of polymers or gel formation or of enormous channels in drug release limiting polymeric barrier. In addition the faster drug dissolution in hydroalcohic media must have synergized the drug release.

Table 1: Model fitting for Metformin SR release

	Water	Mild beer	Strong beer	40% Alcohol	rum
Best Fit	Matrix	Peppas	Peppas	First Order	First Order
N	0.2584	0.2806	0.2471	0.1991	0.2971
K	47.69	50.47	55.09	64.49	52.71
R^2	0.9593	0.9969	0.9940	0.9583	0.9652

In case of Diclofenac sodium from Diclo DR 98% drug release in purified water was observed over a period of one hour suggesting the extension of release profile. The findings of release studies of Diclofenac sodium from Diclot SR 1 formulation indicated almost complete release of drug over a period of ten hours (Fig. 6).

Diclo DR tablets followed the same trend observed for Met IR tablets and the release was in the order strong beer > mild beer > rum ≥ 40 % alcohol. (Fig. 8). The delayed release tablets are typically coated with enteric polymers such as phthalate esters, methacrylic acid copolymers etc. which are soluble in alcohol. Thus, the volume and strength of alcohol has affected the barrier properties of enteric polymers.

In present study, it was found that in case of IR formulation of Metformin hydrochloride, drug release was faster in red wine and white wine as compared to water (Fig. 11). Diclofenac DR followed the same pattern with faster drug release in red wine than in white wine as compared to water (Fig.12). Similar results were obtained in case of SR formulations of Metformin and Diclofenac. Metformn and Diclofenac SR formulation showed faster drug release in red wine than in white wine as compared to water(Fig. 13 and 14). The alcohol content of red wine is 13% and that of white wine is 8% as per the label. Thus, the results of present study indicate that the release of drug depended on concentration of alcohol. The consequences of the changes in the dissolution profiles observed in case of SR formulations would depend on the drug.

Diclofenac SR tablets demonstrated almost identical profile in 40 % alcohol and rum (Fig. 10). However the release was retarded in the media containing strong and mild beer and was found to be least in water . This further confirms the proposition that the stronger the alcoholic beverage the greater the disruption of SR mechanism and faster the release.

The alterations in *in vitro* dissolution profiles of SR formulations of Metformin hydrochloride and Diclofenac sodium are indicative of the probable grave clinical consequences due to dose dumping. In case of Metformin hydrochloride, such dose dumping could result in anaphylactic reactions, lactic acidosis and renal impairment. For Diclofenac sodium, the effects could be allergic reactions, fluid retention and impairment of renal function.

Though the n value in hydroalcoholic media shows anamolus transport of drug release, the n value of 0.5 indicates faster drug release. probably by leaking out of insoluble drug through the polymer gel layer.

As compared to Metformin HCL the lesser drug solubility of Diclofenac sodium in water and may have achieved drug diffusion.

The order fitting n value also suggest that the Diclofenac Na tablets must have been formulated using hydrophilic swellable polymers where as the Metformin tablets might have been prepared using hydrophobic polymers with polar channeling agent that have rapid complete solubility in hydroalcoholic media. However the lower n value of Metformin HCL in water can be explained at this stage.

Table 2: Model fitting for Diclofenac SR release

	Water	Mild Beer	Strong Beer	40% Alcohol	Rum
Best Fit	Matrix	Matrix	Pepaas	Higuchi	Higuchi
N	0.5251	0.1779	0.1664	0.3023	0.3410
K	30.45	56.60	60.21	51.73	46.67
R^2	0.9829	0.9135	0.9166	0.9646	0.9626

2. Statistical analysis

The % drug release in water was compared with that in different hydroalcoholic media and statistical significance was tested using ANOVA followed by Dunnet Multiple Comparison Test. Statistical analysis revealed that the drug release pattern in hydroalcoholic media is significantly different than that in the purified water as $t_{observed}$ is greater than $t_{critical}$ for all four formulations.

Table 3: Statistical analysis table (ANOVA and Dunnet's test) for comparison of drug release from Met SR tablets in the dissolution medium (hydroalcoholic medium) of the present disclosure.

Time in Hours	Source of Variation	Sum of Squares	Degrees of *Freedom*	Mean Squares	F Value	$t_{critical}$
2	Between	233.4	4	58.35	3.9785^{5}	0.0169
	Error	1.4667^{-3}	10	1.4667^{-4}		
	Total	233.4	14			
4	Between	1614	4	403.5	1.9523^{6}	0.0201
	Error	2.0667^{-3}	10	2.066^{-4}		
	Total	*1614*	*14*			
6	Between	1522	4	380.4	2.3774^{6}	*0.0177*
	Error	1.600^{-3}	*10*	1.60^{-4}		
	Total	1522	14			
8	Between	669.4	4	167.3	1.0914^{6}	0.0173
	Error	1.533^{-3}	10	1.5333^{-4}		
	Total	669.4	14			
10	Between	161.4	4	40.35	2.2418^{5}	0.0187
	Error	1.800^{-3}	10	1.800^{-4}		
	Total	161.4	14			
12	Between	19.27	4	4.816	67.99	0.3726
	Error	0.7084	10	7.08^{-2}		

	Total	19.97	14			

$t_{observed} = 2.62$

Table 4: Statistical analysis table (ANOVA and Dunnet's test) for comparison of drug release from Diclo SR tablets in the dissolution medium (hydroalcoholic medium) of the present disclosure.

Time in Hours	Source of Variation	Sum of Squares	Degrees of Freedom	Mean Squares	F Value	$t_{critical}$
2	Between	1827	4	456.6	9.513^{5}	0.0306
	Error	4.800^{-3}	10	4.800^{-4}		
	Total	1827	14			
4	Between	370	4	403.5	4.204^{5}	0.0207
	Error	2.20^{-3}	10	2.066^{-4}		
	Total	370	14			
6	Between	1044	4	260.9	1.118^{6}	0.0212
	Error	2.33^{-3}	10	2.33^{-4}		
	Total	1044	14			
8	Between	1268	4	317.1	2.264^{6}	*0.0165*
	Error	1.40^{-3}	10	1.4^{-4}		
	Total	1268	14			
10	Between	1016	4	254	1.27^{6}	0.0198
	Error	2.00^{-3}	10	2.00^{-4}		
	Total	1016	14			
12	Between	17.94	4	4.484	6.4^{5}	0.037
	Error	7.0^{-3}	10	7.0^{-4}		
	Total	17.94	14			

$t_{observed} = 2.62$

Comparison of dissolution profiles in varied compositions of the *dissolution medium of* the present disclosure **using f2 values:**

For *in vitro* studies Drug release profiles in dissolution medium of the present disclosure containing mild beer, strong beer,40 % alcohol and rum were compared with drug release profile in water and similarity factors were determined.

Table 5: Comparison of drug release profiles; F2 values for in-vitro studies

Formulation	F2 Values in			
	Mild Beer	Strong Beer	Rum	40 % Alcohol
Met IR	15.2	15.5	15.4	15.9
Met SR	16.3	16.0	13.0	13.0
Diclo DR	9.8	7.2	15.4	15.2
Diclo SR	38.5	35.5	16.1	17.5

The F2 values lesser than 50 are suggestive of significant difference in dissolution pattern in the purified water and respective alcoholic beverage. This confirms the effect of alcoholic beverages on *in vitro* drug release. Also, the consistent upper position of curves for alcoholic beverages indicates faster release in hydroalcoholic media as compared to purified water medium.

Ex-Vivo Method Development

Assembly for Ex-vivo Method Development

Everted Sac Technique

The fresh ileum of healthy male goat was obtained from the slaughterhouse in PSS. The tissues were transported under ice to the laboratory. The intestinal contents were removed by washing with ringer solution and the mesenteric residues were dissected out. The procedure described by Wilson and Wiseman for everted sac technique was followed. Pieces of intestine 6-7 cm long were excised from the small intestine. One end of the intestine was ligated to a glass rod end with a piece of sewing thread and the rod was pushed in, to evert the intestine. One end of the intestine was tied to a needle and the opposite end was tied securely. Five ml of solution was inserted with a needle to the inside compartment of the sac. One end of the

everted intestine was tied to an aerator tube and other end with a long syringe left in it is tied to the arm of aerator tube to keep it straight. This assembly with everted sac tied to aerator tube is placed in dissolution apparatus vessel containing dissolution media. Drug permeation profile was studied for Met IR, Met SR, Diclo DR and Diclo SR tablets in water and in media containing strong beer, mild beer, 40 % alcohol and rum. Serial samples of a known volume were taken from the inside compartment by means of syringe at different time intervals and each time, the volume was replaced with fresh solution. The absorbed amounts of drugs (Metformin and Diclofenac) were detected by a spectrophotometer at 233 and 277nm, respectively. The data obtained were analyzed using PCP-DISSO software.

Everted sac technique was used by using fresh ileum of healthy male goat.

The IR and SR tablets show dramatic changes in release profiles as far as the transport of drug across the physiological barrier is concerned.

Mass transport of molecules in a solution or molecular transport across a barrier is normally measured by fluxes. The flux of a solute is simply defined as the mass or number of molecules moving through a given crosssectional area during a given period of time (Birger Brodin, Bente Steffansen)

$$J = X/A\,t$$

where J is the flux of a mass of compound X (conc or % release), moving through across-sectional area A (in our case it is during time t as illustrated in The unit for a flux value could thus be mol cm^2/ min, or alternatively mg cm^2/ h.Where A is kept constant throughout the experiment so equation becomes

$$J = X/t$$

The permeability of Metformin HCl from Met IR tablets in different hydroalcoholic media was shown in Fig. 15 while Fig. 16 depicts the permeability pattern from Met SR tablets.

Table 6: Permeability coefficient –permeation of Metformin HCl from Met IR tablets

dt	Distilled water dx/dtw	Mild Beer dx/dtmb	Strong Beer dx/dtsb	Alcohol 40% dx/dt40a
5	0.0156	0.0196	0.0208	0.018
10	0.0046	0.0047	0.0051	0.0045
15	0.005	0.008	0.007667	0.007467

Table 7: Permeability coefficient –permeation of Metformin HCl from Met SR 1 tablets

dt	Distilled water dx/dtw	Mild Beer dx/dtmb	Strong Beer dx/dtsb	Alcohol 40% dx/dt40a
1	0.166	0.645	0.784	0.549
2	0.166	0.171	0.231	0.1715
2	0.085	0.119	0.0275	0.151
2	0.0505	0.0885	0.1005	0.034
2	0.0175	0.051	0.141	0.0025
3	0.041333	0.16	0.076667	0.174

Similarly, figure 17 depicts the permeability pattern for Diclofenac DR Tablets and figure 18 depicts that of Diclofenac SR tablets.

Table 8: Permeability coefficient –permeation of Diclofenac Na from Diclo DR1 tablets

dt	Distilled water dx/dtw	Mild Beer dx/dtmb	Strong Beer dx/dtsb	Alcohol 40% dx/dt40a
5	0.0156	0.1482	0.1592	0.1204
10	0.0046	0.0899	0.0993	0.0839
15	0.005	0.0104	0.004333	0.0068
15	0.0018	0.011267	0.0194	0.0128
15	0.001467	0.003267	0.02	0.00173

Table 9: Permeability coefficient –permeation of Diclofenac Na from Diclo SR tablets

dt	Distilled water dx/dtw	Mild Beer dx/dtmb	Strong Beer dx/dtsb	Alcohol 40% dx/dt40a
1	0.845	1.425	1.754	0.987
2	0.1395	0.281	0.5455	0.1685
2	0.1505	0.0665	0.1285	0.2705
2	0.2375	0.375	0.224	0.1175
2	0.0385	0.015	0.0525	0.1
3	0.003333	0.021333	0.015667	0.052333

It can be seen from these figures and permeation coefficients that the permeability is increased in following manner: Strong beer> Mild beer> 40% Alcohol > Rum > Water. This rank order is followed by all the formulation irrespective of their solubility or their release behavior.

The enhancement in permeability of goat ileum depends upon the strength and volume of the alcohol used. It is found that the strong beer increases the permeability to the greatest extent followed by mild beer, 40 % alcohol, and water. The greater the volume greater the permeability is the observation is all the cases. When volumes of two beverages are same, the strength of the alcoholic beverage is playing the key role in enhancing the permeation.

The enhancement in permeability is attributable to disturbance of fluid mosaic model of mucosal layer of ileum as well as increased solubility of drugs in alcohol. The enhanced permeability would result in enhanced absorption that may precipitate adverse drug effects.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step,

We claim

1. A novel dissolution medium for analyzing the effect of alcohol on drug release and permeation pattern, said medium comprising:

    a. at least one alcohol containing fluid; and

    b. water,

    said medium characterized in that the concentration of absolute alcohol in said medium is 2.6 wt%.

2. The medium as claimed in claim 1, wherein the alcohol containing fluid is at least one alcoholic beverage selected from the group consisting of beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura, sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The use of the expression "at least" or "at least one" suggests the use of one or more elements or ingredients or quantities, as the use may be in the embodiment of the invention to achieve one or more of the desired objects or results.

The numerical values given for various physical parameters, dimensions and quantities are only approximate values and it is envisaged that the values higher than the numerical value assigned to the physical parameters, dimensions and quantities fall within the scope of the invention and the claims unless there is a statement in the specification to the contrary.

While certain embodiments of the inventions have been described, these embodiments have been presented by way of example only, and are not intended to limit the scope of the inventions. Variations or modifications in the process or compound or formulation or combination of this invention, within the scope of the invention, may occur to those skilled in the art upon reviewing the disclosure herein. Such variations or modifications are well within the spirit of this invention. The accompanying claims and their equivalents are intended to cover such forms or modifications as would fall within the scope and spirit of the invention.

3. The medium as claimed in claim 1, wherein the alcohol containing fluid is at least one medicated alcoholic preparations selected from the group consisting of syrups, asava, and arishta.

4. A process for analyzing the effect of alcohol on drug release and permeation pattern, said process comprising the following steps:

a. preparing a dissolution medium comprising at least one alcohol containing fluid and water, said medium characterized in that the concentration of absolute alcohol in said medium is 2.6 wt%;

b. pouring said dissolution medium into a first compartment of a dissolution apparatus,

   i. said first compartment further comprises at least one everted sac of goat ileum, at least one aerator tube and a shaft; and

   ii. wherein the everted sac of goat ileum of said first compartment comprises water,

c. pouring water into a second compartment of said dissolution apparatus;

   i. said second compartment further comprises at least one everted sac of goat ileum, at least one aerator tube and a shaft; and

   ii. wherein the everted sac of goat ileum of said second compartment comprises water;

d. admixing at least one theoretical dose of at least one dosage form into said first compartment and said second compartment;

e. rotating said shafts of said first compartment and said second compartment at a speed ranging between 50 and 100 rpm;

f. collecting a predetermined amount of samples from said first compartment, second compartment, everted sac of said first compartment and the everted sac of said second compartment, at a predetermined period of time; and

g. subjecting the samples for analysis to obtain the effect of alcohol on drug release and permeation pattern.

5. The process as claimed in claim 4, wherein the method step (f) further comprises

i. selectively replacing said amount of samples into said first compartment using the dissolution medium as claimed in claim 1;

ii. selectively replacing said amount of samples into said second compartment, and the everted sac of said first compartment and the everted sac of said second compartment using water; and

iii. iterating the method steps (f) and (g) for a predetermine period of time to study the effect of alcohol on drug release and permeation pattern.

6. The process as claimed in claim 4, wherein the alcohol containing fluid is at least one alcoholic beverage selected from the group consisting of beer, barleywine, bitter ale, brown ale, mild ale, old ale, pale ale, scotch ale, porter, stout, cask ale, stock ale, fruit beer, lager, pale lager, bock, maerzen, pilsener, schwarzbier, sahti, wheat beer, witbier, cauim, chicha, cider, perry, plum jerkum, huangjiu, icariine liquor, kasiri, kilju, kumis, mead, nihamanchi, palm wine, pulque, parakari, sakura, sake, sonti, tepache, tonto, tiswin, fruit wine, table wine, sangria, sparkling wine, champagne, fortified wine, port, madeira, marsala, sherry, vermouth, vinsanto, absinthe, akvavit, applejack, arak, arrack, awamori, baijiu, borovicka, cachaça, damson gin, sloe gin, horilka, kaoliang, maotai, metaxa, mezcal, neutral grain spirit, ogogoro, ouzo, palinka, pisco, poitin, raki, rakia, slivovitz, rum, shochu, soju, tequila, ţuica, vodka, bourbon

whiskey, canadian whisky, irish whiskey, japanese whisky, rye whiskey, scotch whisky, tennessee whiskey, manx spirit, brandy, armagnac, cognac, fruit brandy, eau-de-vie, schnapps-obstwasser, damassine, himbeergeist, kirsch, poire williams, williamine and liqueurs.

7. The process as claimed in claim 4, wherein the alcohol containing fluid is at least one medicated alcoholic preparations selected from the group consisting syrup, asava, and arishta.

8. The process as claimed in claim 4, wherein the dosage form is in at least one form selected from the group consisting of tablet, capsule, emulsion, suspension, syrup, gel, cake, powder and semisolid.

Name and signature of the applicants

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