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EFFECT OF COW GHEE ON ORAL ABSORPTION OF DRUGS –AN INVITRO COMPARITIVE RESEARCH STUDY

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RESEARCH ARTICLE

ABSTRACT

In ancient India ghee was used as a vehicle in many ayurvedic and medicinal preparations. Ghee has a lot of uses in day to day life and also it improves the permeability of biological membranes and is responsible for enhanced absorption of materials orally as well as percutaneously. This study is carried out in comparative mode that is comparing the absorption of drug from the ghee containing dosage form with the dosage form which do not contain ghee using invitro animal models. The results obtained reveal that the incorporation of cow ghee in the dosage form is able to enhance the absorption of drug. The results obtained reveal that the incorporation cow ghee in the dosage form is able to enhance the absorption of drug. Increase in the fluidity of the membrane facilitates the Transcellular absorption of the drug. Absorption of hydrophilic macromolecules and ionized drugs can be facilitated by allowing Para cellular transport through opening of tight junctions. Free emulsion droplets provide larger surface area and further lipolysis and formation of mixed micelles. Due to all above said reasons ghee containing dosage forms shows better absorption

Keywords :- Ghee , Paracetamol, Absorption,GIT

Introduction

Gastro-intestinal anatomy

In human beings Gastro-intestinal tract consists of three major parts[1]. They are

1. stomach
2. Small intestine which include duodenum, jejunum and ileum.
3. Large intestine which include cecum, colon and rectum.

The total length of human GIT is approximately 8.35 m. small intestine measures nearly 81% of the total GIT. Small intestine is considered as the primary site of drug absorption. Whereas large intestine measures nearly 19% of the total GIT.

Human small intestine has three anatomical modifications which increases the surface area. Plicae circularis or folds of kerckring are the mucosal folds of small intestine which increases the surface area by three times. Plicae circularis bear finger like projections called as villi which increase the surface area by 10 fold. Each villus is provided with microvilli which increase the surface area by 20 fold. Altogether these three structures increase the surface area of the small intestine by 600 times. The large surface area of small intestine serves as the major site for absorption of food, drug molecules and other substances[1and 2].

Intestinal lymph and lymphatic route plays a major role in absorption of highly lipophilic drug substances. In this case hepatic first effect can be avoided by directly targeting the lymphoid tissue. This increases the bioavailability of highly lipophilic drugs. Adding lipophilic vehicles increases the absorption and therefore bioavailability[3].

Oral absorption of drug in pharmaceutical dosage forms depends upon the following factors[4].

- Release of drug from the dosage form and its dissolution in gastrointestinal fluids
- Solubility of the drug
- Permeability of the drug to the intestinal mucosa
- First pass metabolism of the drug

There are three major categories of factors that affect rate and extent of drug absorption[4].

- Physicochemical properties of the drug which include drug solubility, intestinal permeability of the drug, stability, lipophilicity, pKa and particle size etc.
- Physiological factors which include gastrointestinal pH, gastric emptying, small intestine transit time, bile salts, and absorption mechanism etc.
- Dosage form factors such as solution, tablet, capsule, suspension etc.

In case of liquid orals, if they are solutions properties of solute may have effect on drug permeability. Both hydrogen bond potential and the volume of the solutes contribute to the permeability of drug molecules. The nature of the permeability limiting microenvironment within the cell depends upon the properties of the special solute.

Cell membrane is a semi-permeable membrane. It is a lipoid sieve containing number of specialized carrier molecules (transporters) and numerous aqueous channels. These two structures play a major role in drug absorption. The cell membrane itself can act as an absorptive medium for lipophilic drugs[5]. Drugs can get absorbed in to the systemic circulation is by two ways

1. Active transport
2. passive transport

Active transport: This is carried out by means of specific transporters available in the body. Some drugs which are the analogues of some endogenous compounds have specific transporters for their absorption. The transporters belonging to the Adenosine triphosphate binding cassette (ABC) super family and solute carrier (SLC) help in the absorption of some drug molecules[6].

Passive absorption: Passive absorption of drug molecules takes by two common ways[7]. They are

1. Transcellular absorption
2. Paracellular absorption

Transcellular absorption: In this absorption of drugs takes place by passive transfer of drug molecules by passive diffusion. The physicochemical properties of the drug influence the ability of the drug to cross the lipid core of the membrane. More lipophilic drug molecules predominantly follow Transcellular absorption[8, 9, and 10].

Paracellular absorption: In this absorption of drugs takes places by passive diffusion through aqueous pores between the cells at tight junctions. This way of absorption is particularly followed by hydrophilic compounds[8, 9, and 10]. Aqueous pores have the diameter between 3 to 6 Å. As the pore size of the aqueous pore is restricted molecular size of the polar drug is important in utilizing this route of absorption. Therefore, small hydrophilic molecules with the molecular weight less than 200 can get absorbed in this way.

Local blood flow is a strong determinant of the rate of absorption because it continuously maintains the concentration gradient necessary for passive diffusion to occur. For orally administered drugs, remember that the blood supply draining the gut passes through the liver before reaching the systemic circulation. Since the liver is a major site of drug metabolism, this first-pass effect may reduce the amount of drug reaching the target tissue. In some cases, the first-pass effect results in metabolic activation of an inert pro-drug.

Ghee

Ghee, also known as clarified butter, has been utilized for thousands of years in Ayurveda as a therapeutic agent. Ghee was also the preferred cooking oil. In ancient India ghee was used as a vehicle in many ayurvedic medicinal preparations. Cow ghee is having special medicinal interest[11, 12]. It is used as a coating agent in hot molten state in the design of sustained release pellets[13, 14]. Oral consumption of ghee through food is nothing but offering a finest fuel in to the fires of digestion. Ghee cools the body and prevents overheat. Ghee makes internal body organs smooth and soft and also increases secretion of internal juices, which are diminished by aging. Ghee improves intelligence and intellect. It also acts as a lubricant over the walls of GIT and facilitates easy egestion. Ghee is also better in wound healing. Ghee can be used as bath oil and also as moisturizer.

Susruthasamhitha an authentic and most believable ayurvedic text says that panchagavya ghritha can be used in the treatment of hepatitis, epilepsy, fever and even in the treatment of mania[15]. Although panchagavya ghritha is used in the traditional medicine regularly and routinely there is no authentic modern medical literature on the use of panchagavya ghritha. There are some reports on the use of panchagavya ghritha as a base in some preparations[16, 17, 18, 19]. Panchagavya ghritha have anticonvulsant properties but the degree of protection against epilepsy is limited. So it is not sufficient to use it as single

antiepileptic agent. Anticonvulsant action of panchagavya ghritha is not mediated through GABA receptors[20].

Cow ghee is a good source of essential fatty acids. These essential fatty acids regulate prostaglandin synthesis and induce wound healing[21]. Ghee was described as samskaranuvartini in Charakasamhita, a fundamental treatise on ayurveda[22]. It is experimentally roved that high conjugated linoleic acid enriched with ghee increases antioxidant and antiatherogenic potency in female wistar strain rats[23]. Ghee preserve moisture and cause wound healing [24]. Cow ghee is having good regenerative properties. This property might be useful for wound healing and promoting the growth of healthy cells[25].

Ghee is ideal fat for deep frying because its smoke point (where its molecules begin to break down) is 250 °C (482 °F), which is well above typical cooking temperatures of around 200 °C (392 °F) and above that of most vegetable oils. Ayurveda considers ghee to be *sāttvik* (in the "mode of goodness"), when

used as food. Ghee is the main ingredient in some of the ayurvedic medicines. Ghee is included under *catuh mahā sneha* (the four main oils: *ghrita, taila, vasā* and *majjā*) along with sesame oil, muscle fat and bone marrow. Ghee is the drug of choice for the diseases caused by *Pitta Dosha*. There are many Ayurvedic formulations containing ghee, for example, *Brāhmi ghrita*, *Indukānta ghrita*, *Phala ghrita*, etc.

According to ayurveda ghee enhances percutaneous absorption of substances. Being more lipophilic and processing lubricating ghee aids for better diffusion and percutaneous absorption of drugs and other substances which are topically applied.

Though there are 8 types of ghee mentioned in Ayurvedic classics, ghee made of human breast milk and cow's ghee are claimed to be excellent among them. Further, cow's ghee has *medhya* (intellect promoting) and *rasāyana* (vitalizing) properties. In Sri Lankan indigenous medical traditions (*Deshīya Cikitsā*), ghee is included in *pas tel* (five oils: ghee, margosa oil, sesame oil, castor oil and butter tree oil).

Ghee Health Benefits

Ghee is mostly considered unhealthy, but there are few parameters that make pure ghee healthy. Ghee is the perfect choice for healthy cooking. The secret to ghee health benefits comes from its chemistry. Humans need both saturated and unsaturated fats as part of a healthy diet. Ghee contains both 65% saturated fat and unsaturated fat, 25% mono unsaturated fat and 5% poly unsaturated fat. It is rich in nutrition content makes it ideal for loosing weight, improper digestion, lowering cholesterol levels and increasing resistance to disease.

Aids weight loss

- Pure Ghee is very rich source of conjugated Linoleic Acid, which aids in weight loss by increasing metabolism. It also specifically helps to reduce stubborn belly fat.
- CLA in take is also associated with lowering insulin resistance which makes it easier to control weight. It is also associated with enhanced muscle growth, which helps in burning fat and increasing metabolism.
- Pure Ghee contains no hydrogenated oil which are associated with weight gain as it lower metabolism but also interferes with body's ability to ingest and utilize the good fat causing to eat more in order to feel full

Improves Digestion

Ghee is a source of fat soluble vitamins and essential fatty acids making it a great choice for healthy cooking. It is full of vitamins A, D, E, and K. These vitamins are

- fat soluble that they have to be digested with other fat molecules to make it in to our blood stream.
- Ghee has lot of dietary fats but help our body to absorb and make use of these vitamins. Ghee is also said to stimulate the secretion of stomach acids to help with digestion. Fats like butter and oils on the other hand slow down the digestion process.
- Pure Ghee is rich in antioxidants which improves the digestibility of proteins by 36% and increases bio availability by 62% when it is added to vitamin A deficient diet.
- Ghee also aids in absorption of minerals from other foods, increasing the retention of calcium up to 45% and phosphorous up to 57%.It is a safe alternative for people who are lactose intolerant since all the milk proteins have been removed during the clarifying process.

Helps to lower cholesterol level & increases resistance to disease:

- An additional benefit of CLA which ghee is a rich source ,is that it not only lowers cholesterol ,it is believed to significantly reduce total cholesterol, low density lipoprotein and triglycerides.

- CLA intake is also associated with enhancing immune systems, as well as lowering insulin resistance, which can help us to prevent adult-onset diabetes.
- Pure ghee has a high concentration of butyric acid, a fatty acid that contains anti viral properties and is believed to inhibit the growth of cancerous tumors.

Other uses of ghee:

- Ghee has more wound healing property than oil; it also heals the wounds in the mucus lining of the stomach and balances the acid level in the stomach.
- It improves immunity.
- It improves mind power like better decision making, memory power, learning capacity.
- It softness the skin and maintains the beauty of face.
- It protects body from degenerative diseases as it has anti-oxidants.
- Butyric acid, a fatty acid found in clarified butter, it have an anti-viral and anti-cancer properties.
- Ghee is used in ayurvedic medicinal practice to help with ulcers, constipation and the promotion of healthy eyes and skin.
- Ghee is in topical route for the treatment of burns and blisters.
- Ghee increases assimilation and enhances the nutritional value of food.

In situ model

In situ intestinal perfusion model for the study of drug uptake were first introduce in 1960s. In situ perfusion study is very nearer to in vivo study as blood supply, clearance capabilities, nervous innervations remain intact. The animal is anaesthetized and abdomen is exposed. Intestinal loop is cannulated and then the intestine is perfused with an isotonic solution containing the drug whose absorption is to be estimated. Decrease in concentration of drug in perfusing solution is the measure of intestinal absorption of drug[26, 27].

Everted sac

This technique was first described by Wilson and Wiseman in 1954 when they were studying the transport of sugars and amino acids. over a glass rod such that mucosal epithelium with villi form the outer surface and muscular membrane forms the inner surface of the everted sac. The inner compartment is filled with buffer and both ends are tied tightly. Then the sac is placed in the beaker of buffer containing drug whose intestinal absorption is to be measured. Decrease in concentration of drug in buffer is the measure of intestinal absorption of drug[26, 27].

Requirements:

Ghee (for ghee emulsion).
Arachis oil (for oil emulsion).
Paracetamol suspension(marketed product P-125).
Goat intestine.
Gum(tween80).
Paracetamol drug.
Aerators.
Beakers(500ml).
Kreb's buffer (1000ml).

Method of Preparation of Emulsion: Wet gum method

The oil, water and gum are taken in the ratio of 4:2:1 for the preparation of primary emulsion. The drug (1.25g of paracetamol) was mixed with the oil phase for incorporation of drug in to the emulsion. Gum and water are taken in a dry mortar and pestle and triturate it until it forms mucilage. Add oil (arachis oil) drop by drop triturate it until it forms clicking sound and forms nearly white color. Transfer the above formed primary emulsion into volumetric flask and make up final volume up to 50 ml with water. Each 5 ml of emulsion contains 125 mg of paracetamol.

Another emulsion is prepared in a similar way using cow ghee as oil phase instead of arachis oil. Each 5 ml of emulsion should contain 125 mg of paracetamol.

Procedure of experiment with liquid oral:

Collect the goat intestine from a healthy goat and clean it thoroughly with water until all the contents of intestine are cleared. Place that in a freshly prepared saline solution for about 30 min

with aeration. Then the goat intestine is cut into three pieces of length 16cm. At each end of the intestinal piece an organ bath inner tube is inserted and tied tightly without any leak. Then the organ bath inner tubes are fixed to stands such that intestine tied to them looks in form of 'U' loop. The two other intestinal pieces are also arranged in the same manner.

Into the one intestine 10 ml of the paracetamol emulsion prepared by using arachis oil as oil phase (paracetamol emulsion using arachis oil) is transferred. Then it is placed in a beaker containing 300ml of kreb's buffer. Then the amount diffused out of the intestine in to the beaker containing kreb's buffer can be estimated spectrophotometrically.

Into the second intestinal part 10 ml of the paracetamol emulsion prepared by using cow ghee as oil phase (paracetamol emulsion using cow ghee) is transferred. Then it is placed in a beaker containing 300ml of kreb's buffer.

Into the third intestinal part 10 ml of the commercially marketed brand of paracetamol suspension is transferred. Then it is placed in a beaker containing 300ml of kreb's buffer. Supply air to the intestines with the help of aerators in every setup.

The Biopharmaceutical classification system

BCS classifies drug substances in to three major classes based on their solubility and permeability. They are

Class 1: These are the drugs of high solubility and high permeability. Generally these compounds are very well absorbed.

Class 2: These are the rugs of low solubility and high permeability. Generally these compounds exhibit dissolution rate limited absorption.

Class 3: These are the rugs of high solubility and low permeability. Generally these compounds exhibit permeability rate limited absorption.

Class 4: These are the rugs of low solubility and low permeability. Generally these compounds possess very poor bioavailability.

Liquid oral dosage forms include solutions, syrups, suspensions, elixirs and concentrates that provide good patient compliance for those who have difficulties in swallowing and also provide better dosage control when compared to fixed tablet dose. Pharmaceutically, Oral liquids are formulated as solutions, suspensions and emulsions depending on the nature of the active ingredient particularly solubility and stability

Lipid vehicles are suited for liquid formulation of low water soluble drugs coming under class II or IV drugs. Lipid-based formulations are an important tool for water-insoluble drugs as they offer the potential for enhancing drug absorption and oral bioavailability. Lipids provide a wide choice to formulate in different kinds of liquid oral dosage forms like solutions, suspensions, emulsions, self emulsifying system and micro-emulsions etc. lipid formulations may provide an answer for the enhancement of absorption and bioavailability of poorly water soluble drugs by facilitating the formation of solubilized phases. The solubilized phases arise from the intralaminal processing of following the lipid absorption. Co-administration of lipids along with drug materials may show an impact on their absorption pathway.

Intestinal lymph and lymphatic route plays a major role in absorption of highly lipophilic drug substances. In this case hepatic first effect can be avoided by directly targeting the lymphoid tissue. This increases the bioavailability of highly lipophilic drugs. Adding lipophilic vehicles increases the absorption and therefore bioavailability[28, 29, 30].

Several studies reported the increased absorption of poor water soluble drugs when administered in lipid based formulations[31]. The mechanisms behind the improvement of absorption include

1. Increase in the fluidity of the membrane which facilitates the Transcellular absorption of the drug[32].

2. Absorption of hydrophilic macromolecules and ionized drugs can be facilitated by allowing Paracellular transport through opening of tight junctions.
3. Free emulsion droplets provide larger surface area and further lipolysis and formation of mixed micelles.
4. Stimulation of chylomicrons / lipoproteins production[31].

Inhibition of P – glycoprotein and / or CYP450 to increase intracellular concentration of the drug and its residence time.

Conclusion

The results obtained reveal that the incorporation cow ghee in the dosage form is able to enhance the absorption of drug. Increase in the fluidity of the membrane facilitates the Transcellular absorption of the drug. Absorption of hydrophilic macromolecules and ionized drugs can be facilitated by allowing Paracellular transport through opening of tight junctions. Free emulsion droplets provide larger surface area and further lipolysis and formation of mixed micelles. Due to all above said reasons ghee containing dosage forms shows better absorption.

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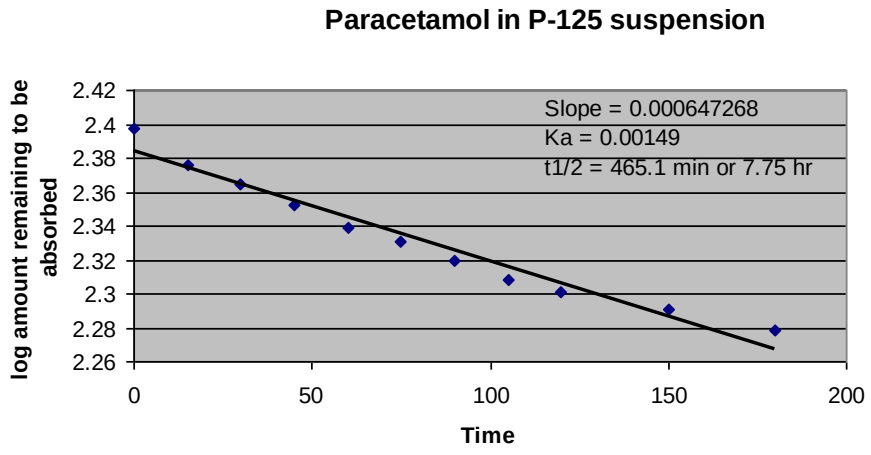

Fig No;- 1 paracetamol in P-125 Suspension

S.No	Time in minutes	Amount of drug absorbed	Amount of drug remaining to be absorbed	log Amount of drug remaining to be absorbed	$t_{1/2}$
1	0	0	250	2.39794	465.1 min or 7.75 hr
2	15	12.6	237.4	2.375481	
3	30	18.58	231.42	2.364401	
4	45	25.136	224.864	2.35192	
5	60	31.67	218.33	2.339113	
6	75	35.814	214.186	2.330791	
7	90	41.124	208.876	2.319889	
8	105	46.416	203.584	2.308744	
9	120	49.932	200.068	2.301178	
10	150	54.604	195.396	2.290916	
11	180	60.08	189.92	2.278571	

Table No:- 1 The absorption of half life of paracetamol in commercially available P-125 suspension was experimentally found to be 7.75hr

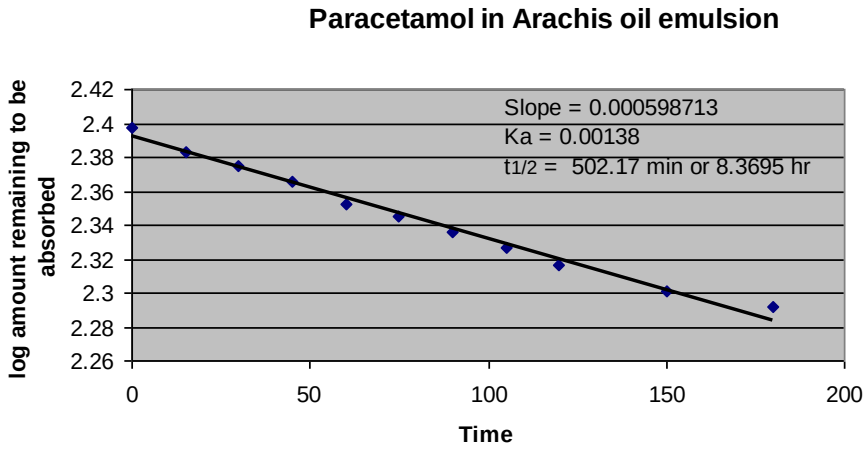

Fig No;-2 Paracetamol in Arachis oil Emulsion

S.No	Time in minutes	Amount of drug absorbed	Amount of drug remaining to be absorbed	log Amount of drug remaining to be absorbed	$t_{1/2}$
1	0	0	250	2.39794	502.17 min or 8.3695 hr
2	15	8.4	241.6	2.383097	
3	30	13.184	236.816	2.374411	
4	45	17.952	232.048	2.365578	
5	60	25.08	224.92	2.352028	
6	75	28.632	221.368	2.345115	
7	90	33.352	216.648	2.335755	
8	105	38.056	211.944	2.326221	
9	120	42.744	207.256	2.316507	
10	150	49.752	200.248	2.301568	
11	180	54.408	195.592	2.291351	

Table no:-2 The absorption of half life of paracetamol in emulsion where arachis oil is used as oily phase was experimentally found to be 8.3695hr.

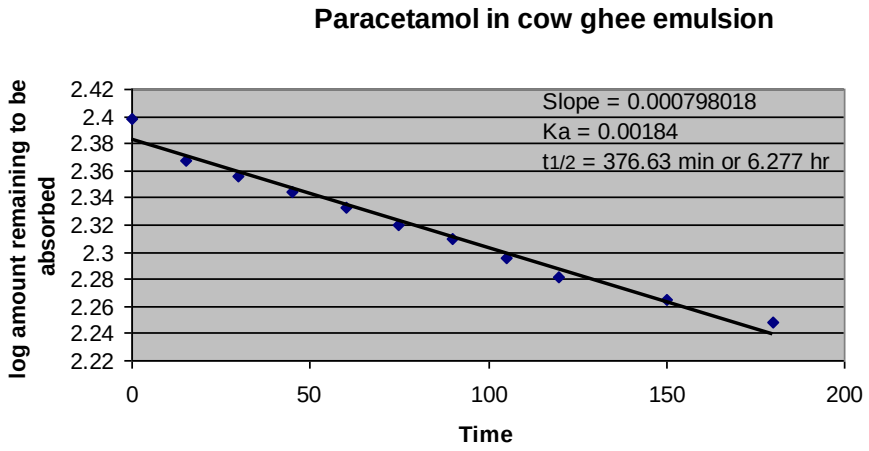

Fig No:- 3 Paracetamol in Cow ghee Emulsion.

S.No	Time in minutes	Amount of drug absorbed	Amount of drug remaining to be absorbed	log Amount of drug remaining to be absorbed	$t_{1/2}$
1	0	0	250	2.3979	376.63 min or 6.277 hr
2	15	16.8	233.2	2.3677	
3	30	22.78	227.22	2.3564	
4	45	28.74	221.26	2.3449	
5	60	34.68	215.32	2.333	
6	75	41.192	208.808	2.3197	
7	90	45.912	204.088	2.3098	
8	105	52.38	197.62	2.2958	
9	120	58.826	191.174	2.2814	
10	150	65.834	184.166	2.2652	
11	180	72.818	177.182	2.2484	

Table no;-3 The absorption of half life of paracetamol in emulsion where arachis oil is used as oily phase was experimentally found to be 6.277 hr. It is less than that of both arachis oil emulsion and P-125 suspension

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