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COW GHEE: AN ENHANCER OF PERCUTANEOUS ABSORPTION

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ABSTRACT:

Ghee, clarified butter, is the natural animal fat obtained from milk. Use of cow ghee in India is as old as Indian culture. Cow ghee does not get spoiled for longer periods as it contains no water. Cow ghee is considered as an excellent base for the preparation of Ayurvedic medicines. The ability of cow ghee to permeate into deeper tissues makes it as an ideal base for preparing Ayurvedic dosage forms. Our work is targeted to estimate the enhancement of percutaneous absorption by cow ghee using isolated goat skin as the animal membrane. Three drugs namely Salicylic acid, Diclofenac diethyl amine and Neomycin sulphate are used for the study. Salicylic acid is formulated as an ointment by replacing lipid base with cow ghee in different proportions (5%, 10%, 15%, 20% and 25%). Salicylic acid ointment without cow ghee (0% cow ghee) is used as a reference for comparison. Similarly, diclofenac diethyl amine and neomycin sulphate are formulated as creams using cow ghee in different proportions (5%, 10%, 15%, 20% and 25%). The fur on the goat skin was shaved and 3g of ointment/cream is applied on it. The other side of the skin is dipped in to the modified krebs buffer solution. Six such experimental setups are made for each drug i.e., one for each concentration of cow ghee (0%, 5%, 10%, 15%, 20% and 25%). The results obtained show the definite increase in rate of absorption and also definite decrease in absorption half life with increase in concentration of cow ghee for all the three drugs. From the results obtained it is clear that cow ghee enhances the percutaneous absorption of drugs. However, further studies like accelerated stability testing are needed to estimate the stability of the dosage form. Adding appropriate preservatives is needed to improve the stability of the preparation.

Key words: Cow ghee, Percutaneous absorption, Skin absorption, Skin permeability, Permeability enhancement.

1. INTRODUCTION:

Ghee, clarified butter, is the natural animal fat obtained from milk. Its use in India is as old as Indian culture. Cow ghee is essential and sacred component required in hindu religious rituals called yagnyas and homas (fire offerings). In this cow ghee is offered to agni (fire). In Yagnyas agni is considered as mouth of god and through him we feed god with ghee. So cow ghee is considered as food of gods. An ancient Indian medical system, Ayurveda, utilizes ghee as a vehicle in many medicinal preparations. Ghee is the oldest known cooking oil in India. Thus, use of ghee is mixed with Indian culture through religion, medicine and kitchen. Indians consume considerable amount of ghee through their diet. Ghee is the most suitable fuel into the fires of digestion. Cow ghee cross the cell membrane and gets absorbed easily. It is also a concentrated source of energy having dietetic value, easier for digestion and absorption. Fats and fatty acids are building blocks of lipids. They are the main components in biological membranes. They offer flexibility and fluidity to cell membranes

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and also helpful in transport of substances across the membrane [1].

Among all edible fats from animal and vegetable sources cow ghee is best digested. Nearly 96% of cow ghee is digested. Most of the Ayurvedic formulations used for the treatment of ailments especially in those which are used for treatment of chronic and degenerative diseases contains cow ghee as an integral part. It is used as an agent that helps for nourishment, extraction, absorption and assimilation.

The pure form of cow ghee is light, oily and do not contain water, lactose and other milk solids. Cow ghee does not get spoiled for longer periods as it contains no water. So refrigeration is not needed for its preservation. According to Ayurveda as ghee becomes older for years its taste may become slightly bitter but its effectiveness and healing properties increases. In many classical Ayurvedic formulations 5 to 10 year old ghee is highly preferred.

Cow ghee is an excellent base for the preparation of Ayurvedic medicines. The ability of cow ghee to permeate into deeper tissues makes it as an ideal base for preparing Ayurvedic dosage forms. Ayurveda described cow ghee as good adjuvant/vehicle for transport of drugs into the deeper areas in the tissue layers of the human body. Human cell membranes contain lipids and cow ghee shows highly lipophilic action. This facilitates the drug to get placed at target cellular level by cow ghee. Cow ghee digests, absorbs and delivers the drug at the target. This is the most crucial thing to take place for getting maximum benefit from the formulation used in therapy.

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 [2]. Cow ghee is useful as an antidote [3]. Cow ghee is useful in enhancement of memory. It possesses nootropic activity. Medicated ghee, Pancha Gavya Gritha (PGG), is superior to plain cow ghee [4]. Optimum use of ghee does not result in CAD. The previous studies involving animal models revealed the dose dependent decrease of Cholesterol levels. That includes HDL, LDL, VLDL, and triglyceride levels. Even 10% ghee in diet did not show any evidence for increased risk of CAD [5][6]. Interestingly a study conducted in the men of rural India has shown the decreased or lesser prevalence of CAD in the men who consume high amount of ghee [7].

Cow ghee contains fat soluble vitamin E and beta carotene which are antioxidants. Panchagavya ghrita is a peculiar combination of five cow products namely dung, urine, milk, curd and ghee [8]. It contains both water soluble and fat soluble antioxidants and acts strong antioxidant and relieves oxidative stress [9]. Panchagavya ghrita can also be used in the treatment of vishamajvara (Malaria/Typhoid) [10], psychogenic and neurogenic disorders [11]. According to ayurveda ghee enhances percutaneous absorption of substances. Being more lipophilic and possessing lubricating property ghee aids for better diffusion and percutaneous absorption of drugs and other substances which are topically applied [12].

Skin is the largest organ of the body. It covers 1.6 m^2 surface area and accounts for 16% of total body weight of an adult approximately [13]. It is a multilayered outer covering of the body and protects all the internal body organs from environmental risk factors. The role of skin is major in offering protection against invading pathogenic species. Skin

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serves as insulation and acts as thermoregulator. It also prevents loss of water from the body. It is a sensory organ and provides the sense of touch.

Skin absorption is a route by which substance can enter the body through the skin. Permeability is the term that refers the process which allows the movement of substances across the biological barriers. Human skin shows high selectivity and low permeability. This property of the skin prevents the entry of foreign particles and microorganisms into the body there by it protect the body invading microorganisms and toxins. Stratum corneum, the outer most layer of the skin performs this function effectively. However, sometimes it is desired to permit the penetration of substances into deeper layers of the skin and even into muscular layers. Inunction is a process of rubbing the medicament against the skin to show systemic action. Some pain killers are rubbed against the skin to relieve deep muscular pains. In such cases drug shows property of penetration and diffusion in to the deeper layers of the skin and even in to the muscular layers. In such cases to facilitate easy penetration of drug molecules, permeation of the skin is to be enhanced. Electroporation, Iontophoresis, Sonophoresis, magnetophoresis, and Microporation are some physical methods used for the enhancement of skin permeation. Along with these physical methods chemical permeation enhancers can also be used [14]. In topically applied dosage forms usually chemical permeation enhancers are used. This alters the barrier property of stratum corneum and facilitates the process of absorption by enhancing the penetration [15]. The chemical agents used as permeation enhancers may produce the desired effect by various mechanisms. They include the interaction of permeability enhancer with the organizational lipids of the skin and resulting in increase in fluidity [16], interaction with intercellular protein and keratin denaturation [17], extraction of lipids from stratum corneum causing the displacement of bound water and loss of horny cells also delamination of stratum corneum [18], enhancement of solubility and increasing partitioning into stratum corneum [19].

Our work is targeted to estimate the enhancement of percutaneous absorption of drugs by cow ghee using isolated goat skin as the animal membrane.

2. METHOD

In 2007 Cetin Tas and etal described a method of studying percutaneous absorption using rat skin as an In vitro animal model. They used de-fibered wistar strain rat skin to study percutaneous absorption [20]. In 2016 Eman Abd and etal described various models for study of percutaneous absorption of drugs. Model of human skin is also one among them. They also mentioned pig skin as a most nearer alternative to human skin [21]. However, for preliminary estimation any mammalian skin can be used. So, we used de-fibered goat skin was used for estimation percutaneous absorption of drugs. We bought freshly excised skin of a goat and removed the hair from the skin using electric hair remover carefully. After careful removal of adhering fat the skin is soaked in saline solution for half an hour before using for percutaneous absorption study.

Ointments and creams with 0% were prepared using Pharmacopoeial procedures. Later some amount of lipid used in procedure is replaced by cow ghee and prepared ointments creams of respective drugs with 5%, 10%, 15%, 20%, 25% cow ghee concentrations. They were used in the study.

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3. RESULTS

The above results show that the increase in concentration of cow ghee increased the rate of absorption of salicylic acid. Absorption halflife (t1/2) decreased considerably with increase in concentration of cow ghee in formulation.

% of Cow Ghee	Salicylic acid	Diclofenac	Neomycin
0	0.002014	0.002581	0.003406
5	0.002418	0.003283	0.003607
10	0.003008	0.004924	0.003756
15	0.003912	0.00627	0.004316
20	0.00544	0.008237	0.00595
25	0.006361	0.01027	0.009631

The above results show that the increase in concentration of cow ghee increased the rate of absorption of Diclofenac diethyl amine. Absorption half life (t1/2) of Diclofenac diethyl amine decreased considerably with increase in concentration of cow ghee in formulation.

% of Cow Ghee	Salicylic acid	Diclofenac	Neomycin
0	344	268	203
5	287	211	192
10	230	141	185
15	177	111	161
20	127	84	116
25	109	67	72

The above results show that the increase in concentration of cow ghee increased the rate of absorption of Neomycin Sulphate. Absorption half life (t1/2) of Neomycin Sulphate decreased considerably with increase in concentration of cow ghee in formulation. All the above obtained results show increase in percutaneous absorption of drugs when cow ghee is incorporated in their formulation. Increase in concentration of cow ghee resulted in increase absorption in all the three drugs.

ANOVA was applied on the value of Ka and t1/2 values of drugs against different concentrations of cow ghee to know whether the obtained values are significant or not. In this, the data is grouped depending on the concentration of cow ghee used in formulation.

From the results of Anova, it is observed that p value is less than alpha value (0.005) and 'F value' is greater than that of 'F critical value' or 'F-statistic'. So, null hypothesis was rejected. The values were considered to have significance.

3. DISCUSSION

From the observed results of the work increase in concentrations cow ghee in ointments and creams had resulted in increase in percutaneous absorption. Though all the ointments and creams contain lipids as base more than them cow had shown increase in absorption across the layers of skin. This may be due to increase in fluidity of

ANOVA : Single Factor on Ka of Drugs						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	8.02E-05	5	1.6E-05	9.627347	0.000699	3.105875
Within Groups	2E-05	12	1.67E-06			
Total	0.0001	17				
ANOVA: Single Factor on $t_{1/2}$ of Drugs						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	77763.61	5	15552.72	7.976891	0.001612	3.105875
Within Groups	23396.67	12	1949.722			
Total	101160.3	17				

membranes across the layers of skin. As a whole, we can conclude that more than commercially used lipids of ointments and creams cow ghee produce better absorption of the drugs across the skin. However, further studies are to be carried out to assess its stability in formulation and it is necessary to find out a suitable preserve to improve the stability of the formulation. As we used goat skin as the model to study percutaneous absorption of drugs in presence of cow ghee, it is also necessary to verify whether the results pattern is same in human models or not.

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5. CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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Table:

Time in minutes	Release kinetics of Salicylic acid in 0% ghee ointment			Release kinetics of Salicylic acid in 5% ghee ointment			Release kinetics of Salicylic acid in10% ghee ointment		
	ADA in µg	ARA in µg	log ARA	ADA in µg	ARA in µg	log ARA	ADA in µg	ARA in µg	log ARA
0	0	60	1.778	0	60	1.778	0	60	1.778
15	2.676	57.324	1.758	3.747	56.253	1.75	3.695	56.305	1.75
30	3.73	56.27	1.750	5.297	54.703	1.738	5.899	54.101	1.733
45	5.834	54.166	1.734	6.95	53.05	1.725	7.418	52.582	1.721
60	8.44	51.56	1.712	8.214	51.786	1.714	10.446	49.554	1.695
75	9.454	50.546	1.704	10.069	49.931	1.698	12.392	47.608	1.678
90	10.973	49.027	1.690	12.365	47.635	1.678	14.879	45.121	1.654
105	12.256	47.744	1.679	14.523	45.477	1.658	17.453	42.547	1.629
120	13.854	46.146	1.664	16.806	43.194	1.635	19.257	40.743	1.610
135	15.567	44.433	1.648	18.957	41.043	1.613	21.387	38.613	1.587
150	17.026	42.974	1.633	20.425	39.575	1.597	23.426	36.574	1.563
`165	18.064	41.936	1.623	21.506	38.494	1.585	25.163	34.837	1.542
180	19.454	40.546	1.608	22.489	37.511	1.574	26.746	33.254	1.522
195	20.552	39.448	1.596	23.354	36.646	1.564	27.627	32.373	1.51
210	21.126	38.874	1.59	24.332	35.668	1.552	28.549	31.451	1.497
225	22.076	37.924	1.579	25.126	34.874	1.542	29.326	30.674	1.487
240	22.756	37.244	1.571	25.989	34.011	1.531	29.965	30.035	1.478
$t_{1/2}$	343.609 min or 5.727 hr			286.649 min or 4.777 hr			230.184 min or 3.836 hr		

Time in minutes	Release kinetics of Salicylic acid in 15% ghee ointment			Release kinetics of Salicylic acid in 20% ghee ointment			Release kinetics of salicylic acid in 25% ghee ointment		
0	0	60	1.778	0	60	1.778	0	60	1.778
15	4.122	55.878	1.747	5.223	54.777	1.739	5.962	54.038	1.733
30	5.564	54.436	1.736	6.436	53.564	1.729	6.899	53.101	1.725
45	7.176	52.824	1.723	8.89	51.11	1.708	9.754	50.246	1.701
60	8.96	51.04	1.708	11.965	48.035	1.6816	12.516	47.484	1.676
75	11.912	48.088	1.682	15.079	44.921	1.652	16.189	43.811	1.642
90	14.397	45.603	1.659	19.843	40.157	1.604	20.663	39.337	1.595
105	17.523	42.477	1.628	23.121	36.879	1.567	24.236	35.764	1.553
120	20.611	39.389	1.595	27.046	32.954	1.518	28.343	31.657	1.5
135	24.76	35.24	1.547	31.108	28.892	1.461	32.545	27.455	1.439
150	26.46	33.54	1.526	33.768	26.232	1.419	34.826	25.174	1.401
`165	28.723	31.277	1.495	35.528	24.472	1.389	37.023	22.977	1.361
180	30.523	29.477	1.469	37.429	22.571	1.353	39.472	20.528	1.312
195	31.894	28.106	1.449	39.106	20.894	1.320	41.336	18.664	1.271
210	33.114	26.886	1.429	40.118	19.882	1.298	43.874	16.126	1.207
225	34.065	25.935	1.414	41.077	18.923	1.277	44.827	15.173	1.181
240	34.989	25.011	1.398	41.957	18.043	1.256	45.684	14.316	1.156
$t_{1/2}$	177.174 min or 2.95 hr			127.472 min or 2.124 hr			108.967 min or 1.816 hr		

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Table:

Time in minutes	Release kinetics of Diclofenac diethyl Amine in 15% ghee cream			Release kinetics of Diclofenac diethyl Amine in 20% ghee cream			Release kinetics of Diclofenac diethyl Amine in 25% ghee cream		
	ADA in µg	ARA in µg	log ARA	ADA in µg	ARA in µg	log ARA	ADA in µg	ARAin µg	log ARA
0	0	5000	3.698	0	5000	3.698	0	5000	3.698
15	348.21	4651.79	3.667	395.09	4604.91	3.663	455.36	4544.64	3.657
30	676.34	4323.66	3.635	783.48	4216.52	3.624	904.02	4095.98	3.612
45	1011.16	3988.84	3.6	1158.48	3841.52	3.584	1345.98	3654.02	3.562
60	1332.59	3667.41	3.564	1513.39	3486.61	3.542	1734.37	3265.63	3.513
75	1547.32	3452.68	3.538	1854.91	3145.09	3.497	2102.68	2897.32	3.461
90	1941.96	3058.04	3.485	2169.64	2830.36	3.451	2450.89	2549.11	3.406
105	2216.52	2783.48	3.444	2464.28	2535.72	3.404	2772.32	2227.68	3.347
120	2470.98	2529.02	3.402	2738.84	2261.16	3.354	3087.05	1912.95	3.281
135	2705.35	2294.65	3.36	3000	2000	3.301	3381.69	1618.31	3.209
150	2919.64	2080.36	3.318	3241.07	1758.93	3.245	3595.98	1404.02	3.147
`165	3107.14	1892.86	3.277	3468.75	1531.25	3.185	3803.57	1196.43	3.077
180	3274.55	1725.45	3.236	3676.34	1323.66	3.121	4011.158	988.842	2.995
195	3421.87	1578.13	3.198	3870.53	1129.47	3.052	4191.963	808.037	2.907
210	3549.1	1450.9	3.161	4044.64	955.36	2.98	4345.98	654.02	2.815
225	3790.18	1209.82	3.082	4191.963	808.037	2.907	4473.213	526.787	2.721
240	3877.23	1122.77	3.05	4305.803	694.197	2.841	4587.05	412.95	2.615
t1/2	110.6269 min Or 1.84 hr			84.1365 min Or 1.4 hr			67.5 min Or 1.125 hr		

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Table:

Time in minutes	Release kinetics of neomycin in 0% ghee cream			Release kinetics of neomycin in 5% ghee cream			Release kinetics of neomycin in 10% ghee cream		
	ADA in µg	ARA in µg	log ARA	ADA in µg	ARA in µg	log ARA	ADA in µg	ARA in µg	log ARA
0	0	5000	3.698	0	5000	3.698	0	5000	3.698
15	107	4893	3.689	383.75	4616.25	3.66	464	4536	3.656
30	635.03	4364.97	3.639	763.11	4236.89	3.62	844.56	4155.44	3.618
45	886.64	4113.36	3.614	1013.21	3986.79	3.6	1104.39	3895.61	3.59
60	1129.25	3870.75	3.587	1259.98	3740.02	3.57	1348.79	3651.21	3.562
75	1358.88	3641.12	3.561	1491.58	3508.42	3.54	1579.56	3420.44	3.534
90	1533.59	3466.41	3.539	1671.91	3328.09	3.52	1758.72	3241.28	3.51
105	1712.23	3287.77	3.516	1853.34	3146.66	3.49	1939.57	3060.43	3.485
120	1928.3	3071.7	3.487	2062.04	2937.96	3.46	2158.35	2841.65	3.453
135	2057.72	2942.28	3.468	2201.78	2798.22	3.44	2290.23	2709.77	3.432
150	2170.43	2829.57	3.451	2315.58	2684.42	3.42	2405.15	2594.85	3.414
`165	2302.21	2697.79	3.431	2440.97	2559.03	3.4	2539.14	2460.86	3.39
180	2399.23	2600.77	3.415	2549.23	2450.77	3.38	2638.91	2361.09	3.373
195	2507.92	2492.08	3.396	2649.65	2350.35	3.37	2748.47	2251.53	3.352
210	2606.31	2393.69	3.379	2750.68	2249.32	3.35	2849.96	2150.04	3.332
225	2697.31	2302.69	3.362	2843.69	2156.31	3.33	2943.34	2056.66	3.313
240	2788.89	2211.11	3.344	2945.72	2054.28	3.31	3046.54	1953.46	3.29
$t_{1/2}$	203.46 min Or 3.39 hr			193.44 min Or 3.20 hr			185.26 min Or 3.08 hr		

Time in minutes	Release kinetics of neomycin in 15% ghee cream			Release kinetics of neomycin in 20% ghee cream			Release kinetics of neomycin in 25% ghee cream		
0	0	5000	3.69	0	5000	3.69	0	5000	3.69
15	562.25	4437.75	3.647	705.07	4294.93	3.63	847.87	4152.13	3.618
30	908.17	4091.83	3.619	1159.78	3840.22	3.58	1340	3660	3.563
45	1213.52	3786.48	3.578	1405.65	3594.35	3.55	1659.41	3340.59	3523
60	1486.69	3513.31	3.545	1663.23	3336.77	3.52	2036.01	2963.99	3.471
75	1700.5	3299.5	3.518	1896.92	3103.08	3.491	2381.19	2618.81	3.418
90	1800.68	3199.32	3.505	2115.33	2884.67	3.46	2694.53	2305.47	3.362
105	1999.99	3000.01	3.478	2282.55	2717.45	3.434	2948.85	2051.15	3.311
120	2183.48	2816.52	3.449	2469.33	2530.67	3.403	3187.82	1812.18	3.258
135	2342.2	2657.8	3.42	2711.59	2288.41	3.359	3333.82	1666.18	3.205
150	2493.61	2506.39	3.399	2876.1	2123.9	3.322	3583.89	1416.11	3.151
`165	2646.51	2353.49	3.371	3042.21	1957.79	3.291	3766.85	1233.15	3.091
180	2791.99	2208.01	3.34	3290.25	1709.75	3.232	3942.6	1057.4	3.024
195	2938.86	2061.14	3.314	3469.47	1530.53	3.184	4119.96	880.04	2.944
210	3078.17	1921.83	3.28	3632.54	1367.46	3.135	4289.999	710.001	2.888
225	3218.2	1781.8	3.25	3788.2	1211.8	3.083	4452.648	547.352	2.73
240	3351.8	1648.2	3.217	3927.39	1072.61	3.03	4627.047	372.953	2.57
$t_{1/2}$	160.86 min Or 2.68 hr			116.47 min Or 1.94 hr			72 min Or 1.2 hr		