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Formulation and Preparation of Theophylline "Sonophoric Gel"

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ABSTRACT

Purpose: This study was conducted to investigate gel rheology and extent of drug release across a microfilm (simulating a biological membrane), under the influence of ultra sound energy & dissolution along with determining changes in potency, gel syneresis and gel swelling over 60 days.
Materials and Methods: In the study the sonophor gel was formulated and prepared following the process as described by Lloyd, 2005 where carbopol (934) was used as a gelling material and plain distilled water was used as the solvent. The formula was customized and the drug used in the formula was theophylline (anhyd.) taken in an amount of 1%.
Results: Study results showed pseudoplastic flow of the sonophor gel and exponential term of the plot was found greater than unity. Tests involving determination of extent of drug release across a microfilm (simulating a biological membrane), under the influence of ultra sound energy & dissolution, results showed although the presence of microfilm reduced extent of drug release yet sonication increased drug release by many folds irrespective of the presence and absence of the microfilm barrier. Regarding dissolution, extent of drug release was 17% in 45 minutes. Regarding investigation on changes in gel potency, gel-syneresis and gel-swelling over the specified time period results failed to show noticeable changes in potency and there occurred no gel-syneresis and no gel-swelling.
Conclusion: It is possible to formulate and prepare a stable Theophylline "Sonophoric gel" which might be used as an alternative for asthmatics when results would be simulated further for clinical studies

Key words: Gel, Sonophor, theophylline, rheology and extent of drug release

INTRODUCTION

'Gels' are regarded as dispersions of liquids within solids. [1] At present 'gels' are popularly used as dosage form and has drawn attention in research and medical fields. [2-4] The major benefits of gels are that these can be self administered avoiding the use of instrumental assistance (like syringe and needle) and or a medical practitioner (like compounder). Termination of therapy can be done at patient's will and here side effect(s) of drug(if any) is minimal and most importantly drugs undergoing fast pass metabolism and rapid chemical degradation due to gastric pH or gastric enzyme, gels serves as the better option for them. Gels are soft to touch, miscible with skin's watery exudates and do not produce stickiness as seen with ointments, creams (w/o) and balms. [5] For targeted drug delivery systems gels opened a new era [3,4,6] indeed, yet 'gels' are not without criticism(s) because skin penetration serves as a major limitation of gel therapy. Skin of our body prevents free entry of foreign particles and keeps us safe and protected from health hazards. In order to overcome such limitation several approaches have been adopted and the use of ultrasonic energy source is one of them. [7] The energy from the ultrasound source disrupts lipid packing of intercellular spaces present in stratum corneum due to heating and cavitation effects and this ultimately enhances drug penetration into the tissues and sets rapid onset of drug action. [7] Asthma is a chronic inflammatory disorder

of the airways that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing. The condition is characterized by increased responsiveness of the trachea and bronchi to a variety of stimuli. It is reported that such causative stimuli may be common allergens (like pollen grains), some foods (like prawns), chemical fumes and air pollutants, in some cases it may be drug induced. [8, 9] In recent times the incidence of asthma has increased tremendously. It is reported that about 334 million of the world's population are now affected by asthma and the prevalence is much higher for both children and elders. Asthma has been designated as the 14th most important disorder in the world in terms of the extent and duration of disability and currently has been regarded as a social and financial burden. [10] In the context of Bangladesh ~ 7 million people of the total population including 4 million children are suffering from asthma. [8, 9] Situation has become more complicated as asthma lacks curative medication. Asthma can be only controlled and managed if the patient follows the set guide lines as suggested by the Health Care providers. [11] In the management of asthma a number of drugs are used and theophylline is one of them. [9,12] Theophylline is chemically known as dimethyl xanthine and pharmacologically has been classified as a bronchodilator. Although the exact mode of action of this drug in asthma is still unclear but interestingly the drug is in use till today. This drug is well tolerated by the body and has an established pharmacokinetic parameters. Therefore this drug has been used as a model drug in research. [13-18] In local market theophylline is available in various dosage forms including tablets, dry powder inhalers, elixirs, solutions and injectables. [12] Unfortunately these forms contain a large number of glucogenic excipients (like starch, glycerin, sorbitol, sucrose and lactose) which may impose a big burden for the diabetic patients. It is well agreed that the prevalence of diabetes is alarming. [19,20] Under such circumstances topical preparation like 'gel' may be the better option for the diabetic asthmatics. Thus this study aimed at the formulation and preparation of a sonophor gel containing theophylline and also to investigate gel rheology, drug release kinetics across a microfilm (simulating biological skin), under the influence of ultrasound energy and gel dissolution.

In the study rheology was given preferences as gels upon application makes a film on the skin and filming may be 'Newtonian' or 'non Newtonian'. For 'Newtonian' rheology the applied force per unit area meaning shearing stress (f) produces a proportionate change in rate of shear (G) signifying proportionate flow. So the rheogram as plotted G versus f will be linear. Otherwise it will be 'non-Newtonian' where changes in G due to changing f will not be proportional. Rather would be disproportionate and the rheogram will be accompanied either by an exponential term or a yield value. [21,22] In general a rheogram accompanied by an exponential term signifies a non linear, exponential change in G as f is changed; while a rheogram accompanied by a yield value signifies a limiting value of shearing stress beyond which flow occurs. Knowledge about gel rheology was therefore important to investigate. Apart from knowing gel rheology in this study drug release kinetics of drug from the gel were also felt important to investigate. It is stated earlier, in that, skin penetration is a major criticism of gel preparation and ultra sound energy in many instances enhances drug penetration through the skin. [7] Therefore it was necessary to assess drug release across an artificial membrane and also to assess the positive influence of ultra sound energy on drug release from the sonophor gel. Besides, dissolution test conventionally is carried out to give a measure of extent of drug release from the preparation. Lastly in the study physicochemical properties of the gel were evaluated including 'potency' and occurrence of time dependent 'gel-syneresis' and 'gel-swelling' were checked

periodically. To the best knowledge of awareness of the authors such study has not been done before.

MATERIALS AND METHODS

Materials

Theophylline (anhyd.), carbopol (934), methyl paraben, polyethylene glycols and methanol

Methods

A) Preparation of sonophor gel

In the study the sonophor gel was prepared following the process as described by Lloyd, 2005 where carbopol (934) was used as a gelling material and plain distilled water was used as the solvent. [23] The formula was customized and the drug used in the formula was theophylline (anhyd.) taken in an amount of 1%. Prior to mixing the drug to carbapol gel, the drug was dissolved in a solvent system comprised of methanol and water (50:50). Mixing was done thoroughly until the mass became homogenous, smooth and free from grittiness. Following sonication for 5 minutes, the prepared 'sonophor gel' was taken in an air tight container and was preserved under normal condition until analysed.

B) Tests on 'sonophor gel':

i) Gel- rheology

A certain amount of gel was taken on a glass slide covering an area of unit square cm. A cover slip was placed over the gel and a weight was placed on the cover slip to make a change in area. The process of adding of weights was continued and the respective changes in areas were noted until the gel collapsed. Here weights represented f and changes in areas represented rate of shear (ΔG). The rheogram plotted using ΔG versus f indicated gel- rheology. [1,22]

ii) Determination of extent of drug release

In the study the extent of drug release across a micro film, under the influence of ultrasound energy and dissolution test was determined according to the methods as follows:

a) Method using microfilm

A certain amount of gel was taken in a pouch made up with very fine polyethylene membrane (thickness 20 micron) and the pouch was dipped into plain dist. water (20 ml) kept in a beaker under normal condition. Water was occasionally stirred using a magnetic stirrer at a slow r.p.m up to 30 mins. Water samples (2 ml) were taken out after repeated time interval and were analysed for drug content using a UV/Vis spectrophotometer (Shimadzu 1600) where sample absorbance was read at λ_{max} 214 nm. The unknown concentrations of samples were calculated out from a standard calibration curve drawn with known strengths ranging from 1 to 80 mcg /ml. Here concentration determined was cumulative. In the study gel without microfilm was also analysed following the process as stated above and was treated as control.

b) Method using sonication

In order to investigate the effect of sonication on drug release process adopted was similar as above with the exception in that the beaker containing the pouch was placed in an ultrasound bath (DEON FS minor ultrasonic ltd, England). Sonication was continued for 30 minutes under normal condition.

c) Dissolution test

In the study gel-dissolution test was carried out by using "Rotary basket' method where plain distilled water was used as the dissolution media. [24,25] Dissolution study was continued for 45 minutes. Amount of drug released at different time intervals were determined using the method as described earlier.

iii) Short term stability testing

A short term stability testing spanning a time period of sixty days was done on the sonophor gel. In the test 'gel potency', occurrence of 'gel syneresis' and 'gel swelling' under normal condition was determined. [26]

a) Potency determination

Potency signifies the actual amount of drug in the preparation and this amount should represent drug amount as declared on the label. It is a well established fact that a number of environmental factors (*viz* light, heat, humidity) and chemical factors (*viz* oxidation, hydrolysis, inter ingredient chemical interaction) causes drug degradation and hence loss of potency. [21] So it was important to determine potency at regular time interval. Potency was determined using the method as described earlier using carbopol as a blank.

b) Gel – syneresis test

This term is similar to bleeding that occurs in table jellies and gelatin desserts. It is reported that many gels often undergo contraction either spontaneously or slowly and exudes some fluid that gives rise to consequent squeezing out effect. This leads to continuous coarsening of the matrix or fibrous structure of gel causing hardening of its consistency. This phenomenon is called 'gel syneresis'. Following such 'gel syneresis' the gel ultimately suffers a change in rheology and thermodynamic stability. Therefore 'gel syneresis' is an important property to investigate. In the test method 5 human volunteers (of same age group irrespective of gender and sex) participated and they investigated the gel visually for sixty days. Later on comments of the volunteers were recorded for data interpretation. [27]

c) Gel – swelling test

Gel - swelling is the reverse phenomenon of 'gel syneresis'. In fact a gelling agent is the basic material for making a gel. But the agent when comes in contact with a solvating liquid then an appreciable amount of the liquid may be taken up by the agent and the phenomenon may increase bulk volume of gel. This is 'gel swelling' which results due to 'gel - solvent' interaction. The more the interaction the less would be strength of linkages that lies between the individual molecules of the gelling agent causing a loss in the structural integrity. In the present study 'gel swelling' was also checked following the method as stated about 'gel - syneresis'.

RESULTS

In our study a sonophor gel containing theophylline was prepared using a customized formula and then properties were evaluated. Gel rheology, the extent of drug release and gel potency was given the preferences during evaluation of gel properties. Figure 1 represents carbopol gel, Figure 2 represents gel rheogram and it showed a non Newtonian flow of the gel.

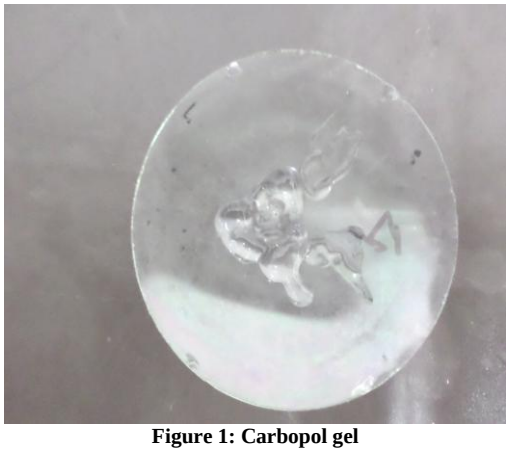

Figure 1: Carbopol gel

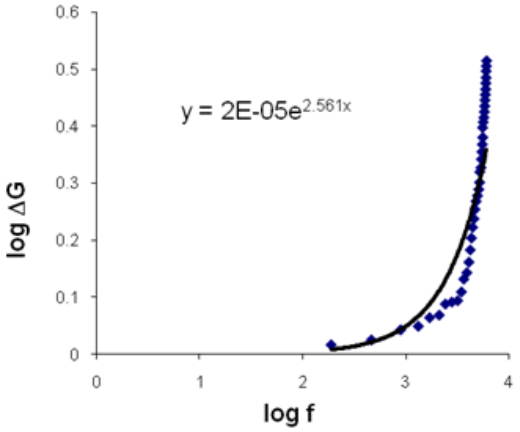

Figure 2: Rheogram for sonophor gel

In the study extent of drug release from the gel was determined firstly in presence of a micro film barrier. Results of the test have been shown in Table 1.

Table 1: Pattern of drug release across the microfilm and under Sonication

Tests	Amount of drug released (mg)	% drug released	Time duration (min)	Conclusions
In water without microfilm & without sonication	0.94 ± 0.53	1.83± 1.00	30	Drug is released from gel in measurable quantity in half an hour.
In water without microfilm & with sonication	0.96 ± 0.34	1.886 ± 0.64	Ibid	Sonication increases drug release from the gel.
In water with microfilm	0.003±0.00	0.006±0.002	Ibid	Micro film retards drug release
In water with microfilm & with sonication	0.064 ±0.01	0.127 ±0.025	Ibid	Sonication increases drug release across the microfilm

Foot note: Values have been rounded off and have been given as mean ± SD (n=2).

Dissolution test was conducted on gel and results are shown in Table 2, which shows ~ 17% drug release in 45 munites.

Table 2: Extent drug release in dissolution test

Time (min)	Initial concentration (mcg /ml)	Cumulative Sample concentration (mcg/ml)	Percent drug release
1		1.99	9
15		2.85	13
30	22.24	3.28	15
45		3.88	17

Foot note: Values have been rounded off

The test on potency was continued for 60 days, results did not show any noticeable changes in the parameter (Figure 3).

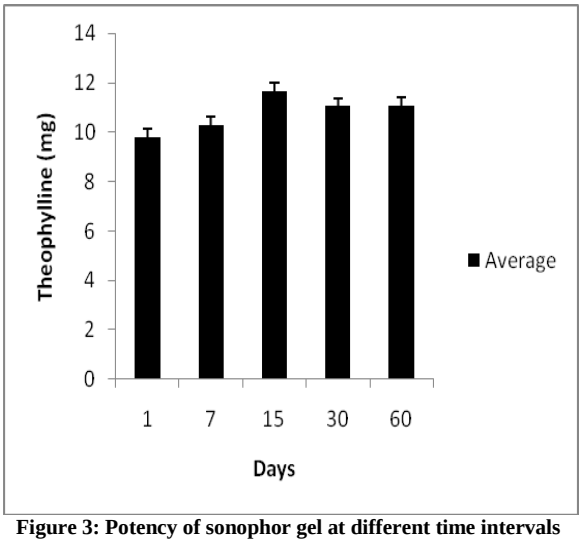

Figure 3: Potency of sonophor gel at different time intervals

Results of 'gel swelling' have been shown in Table 3. In the study 5 human volunteers participated, they investigated the gel visually for the occurrence of 'syneresis' and 'swelling' in the gel over the time period.

Table 3: Testing of gel syneresis and gel swelling

Tests	10 days	20 days	30 days	60 days	120days
Syneresis of gel	NS	NS	NS	NS	NS
Swelling of gel	NS	NS	NS	NS	NS

Foot note: NS signifies noticeable changes were not seen

DISCUSSION

In the study the rheogram (Figure 1) was constructed with ΔG versus f (values being taken on log scale) and relationship between the two parameters was found exponential. The exponent term was found greater than unity signifying pseudoplastic flow. [21] According to Martin *et al*, 1993 and Carter, 1987 polymers in solution exhibits pseudoplastic flow. Usually the rheogram for a pseudoplastic material begins at the origin (or at least approaches at which low rate of shear lies, where yield value is lacking). This makes the rheogram non linear and at this point resistance of the material decreases with increase of rate of shear. Here the curved rheogram results from a shearing action on the long chain molecules of a linear polymer. As f increases it starts the normally disarranged molecules to align the long axes in the direction of flow causing a decrease in the internal resistance of material and allows a greater rate of shear at each successive shearing stress. Carbopol is a high molecular weight synthetic polymer of acrylic acid, cross linked with allyl sucrose and containing a high proportion of

carboxyl group. [28] Aqueous solution of carbopol is acidic, viscous and can be neutralized easily and can be used for many purposes. [28] In the present study it was used as a gelling material. Therefore, the rheogram was found pseudoplastic and in general agreement with others. Table 1 shows that presence of the film restricted drug release significantly (@ 5% level of significance, Mann Whitney 'U' test (one tailed). [29] When the film was absent, drug release was 1.83% ± 1.00 (n=2) and when the film was present, percent drug release came down to 0.006% ± 0.002 (n=2) which was many times less than the value of the former (Table 1). Such results were in general agreement, in that, the film acted like a barrier against flow and reduced the extent of drug release. Regarding the effect of sonicationon on drug release it was reported earlier, in that, ultrasound energy improves release kinetics. [24] Therefore in the present study the effect of sonication on drug release was investigated and investigation was done in the presence and in absence of a barrier. Results are shown in Table 1 and it shows sonication significantly increased drug release in both the cases (@ 5% level of significance, Mann Whitney 'U' test (one tailed). [29] Sonication increased drug release from 1.83% ± 1.00 (n=2) to 1.89% ± 0.64 (n=2) when only water was present and barrier was absent. And when barrier was present sonication also significantly increased drug release from 0.006% ± 0.002 (n=2) to 0.13% ± 0.03 (n=2) (Table 1) (@ 5% level of significance, Mann Whitney 'U' test (one tailed); [29] Such results are as were highly expected. Sonication improved drug release which might be due to either heating or capitation effect or both. [1, 22, 24] Therefore, further study might be simulated for *in vivo* study for future reference.

Table 2 suggests inclusion of drug release promoter in the formulation or modification of the present formulation. It was stated earlier, a short term stability testing under normal condition was done where 'gel potency', 'gel syneresis' and 'gel swelling' were investigated. Results regarding 'gel potency' have been shown in Figure 3 and it shows no noticeable changes in potency over the time period (@ 5% level of significance. [30] A change in potency means occurrence of time dependent changes in the drug amount. And if the change occurs in a decrease order it may suggest drug degradation due to either chemical interaction or environment.

It was stated earlier that 'gel syneresis' is a phenomenon that resembles bleeding in tablets and jellies. In 'gel syneresis' fluid exudation occurs from the preparation and it causes gradual hardening of the matrix rendering the preparation unsuitable to use. [1,2] In the present study 'gel syneresis' was checked over a period of 60 days and results (Table 3) did not show 'gel syeneresis' over that period. Similar was the case with 'gel swelling' which is a reverse phenomenon of 'gel syneresis'. Results did not show 'syneresis' and 'swelling' of the gel. Such results were encouraging and in favour of formulating sonophor gel containing theophylline.

CONCLUSIONS

Therefore, based on our results it may be concluded that it is possible to formulate and prepare theophylline containing sonophor gel. Additionally, if this gel is proven clinically effective then the formulated preparation can be used for treating diabetic asthmatic patients in the years to come. It is stated earlier that topical administration of drugs offers many advantages. Unfortunately for anti-asthma drugs like theophylline such effort has not been tried as per knowledge goes. Therefore this would open up a new area to explore.

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