Original Article

Comparison of Release Retardant Effect of Some Novel Lipids by Formulating Sustained Release Tablet of BCS Class 1 Drug

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ABSTRACT

Aim: The study was carried out with the objective of comparing the release retardant effect of some novel lipids by preparing sustained release tablets of highly water-soluble drug, theophylline. **Methods:** The tablets were a mixture of theophylline and each of the three novel lipids taken in different ratios (Compritol ATO 888, Precirol ATO 5, Dynasan 114) prepared by Direct compression method. Drug and novel lipids interaction was determined by FTIR spectroscopy and DSC while drug release from the sustained release tablets was studied using USP-II dissolution apparatus. The release was analysed to determine the lipid showing the best retardant effect. It was also subjected to different kinetic models to evaluate the release kinetics and mechanism of release. Statistical analysis was done on *in-vitro* release data by ordinary one-way ANOVA to check for significant difference in release for different formulation. The hardness and other evaluation parameters of the tablets were within acceptable range. **Results:** FTIR and DSC showed no interaction between the drug and the lipids of the formulations (DC1 to DC9) and DC1 formulation showed the best sustained release in 12 hr. The result of release retardant effect given by the lipids is in the order dynasan < precirol < compritol. **Conclusion:** The study showed that Compritol ATO 888 (glyceryl behenate) was highly hydrophobic lipid and therefore showed best sustained release of water-soluble drug theophylline as compared to Precirol ATO 5 (glyceryl palmitostearate) and Dynasan 114 (glyceryl tri myristate) lipids.

Key words: Theophylline, Direct Compression, Sustained Release, Compritol ATO 888, Precirol ATO 5, Dynasan 114.

INTRODUCTION

Any drug or dosage form modification prolonging the therapeutic activity of drug can be defined as a sustained release dosage form.[1] The principal objectives of sustained drug delivery are safety, enhancement of efficacy of drug and better patient compliance. Sustained drug delivery systems are becoming popular in the treatment of acute and chronic diseases because of maintenance of concentration of drug in plasma above the minimum effective concentration and below the maximum safe level for an extended period of time. Thus, sustained drug delivery systems achieve optimum drug therapy with reduced dosing frequency and reduced side effects.[2]

Theophylline (BCS class-1) is a methyl xanthine drug, clinically used as bronchodilator and in asthma usually as oral formulations.[3] Its action as non-selective inhibitor of cyclic nucleotide phosphodiesterases causes relaxation of the airway smooth muscle cells, making it useful in the treatment of asthma and COPD (chronic obstructive pulmonary disease).[4-6] Its biological half- life is 3-4 hr and it has a narrow therapeutic concentration range of 10 to 20 µg/mL. Toxicity typically appears at concentration above 20 µg/mL but fluctuations in its serum concentrations may cause variability in clinical response. Theophylline was selected as the model

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drug to study the release retardant effect of the three novel lipids as it a highly soluble BCS class-1 drug.[7,8]

Lipids are biological molecules showing limited aqueous solubility and also hampered solubility in non-polar organic solvents. They have dominant intermolecular hydrophobic and van der Waals interactions. However, some lipids are amphipathic in nature, interacting via hydrogen bonding and electrostatic interactions with aqueous based solvents.[9,10] Novel lipids are the new chemical entities, designed using increasingly available receptor structural information.[11] Novel lipids are increasingly being used for modification of drug release from dosage forms because of their inertness resistance to changes in drug release on change in pH.[12]

Till date several studies have been carried out by using novel lipids in sustained release dosage form. Sustained release tablet of drug Etoricoxib,[13] Aceclofenac,[14] Glipizide[15] have been formulated using lipids like glyceryl monostearate and glyceryl behenate for Etoricoxib, Compritol for Aceclofenac and Compritol and stearic acid for Glipizide, for studying the release retardant effect of lipids used.

Kalakuntta *et al.* carried out a study using theophylline as the drug and compritol ATO 888, Precirol ATO 5 and Geleol as lipids revealing Compritol to be the lipid sustaining the release to the greatest extent. Janin *et al.* also formulated theophylline sustained release tablet using Compritol ATO 888 as release retardant but different pore forming agents like lactose or dibasic calcium phosphate anhydrous.[16]

Theophylline sustained release tablet were also formulated using dika fat and Minitab using Compritol ATO 888, showing these lipids to successfully retard the release of drug.[17]

But no study has been conducted, so far, comparing the release retardant effect of Compritol ATO 888, Precirol ATO 5and Dynasan 114 on theophylline, it being a highly Soluble BCS class I drug.

So, in this research novel lipids Compritol ATO 888 (glyceryl behenate), Dynasan 114 (glyceryl trimyristate) and precirol ATO 5 (glyceryl palmitostearate) were used for formulating sustain release tablets of theophylline by direct compression method. Each novel lipid was used at three levels of drug: lipid ratio (100:100, 100:125, 100:150) for preparing tablets. The tablets prepared were subjected to *in-vitro* drug release to determine the release retardant effect of lipids in sustaining the release of drug. The lipid showing the least *in-vitro* release at the end of testing period was considered to possess the best potential for sustaining the release of the drug.[18,19] Composition of various batches has been shown in Table 1.

MATERIALS AND METHODS

Materials

Theophylline was obtained from Yarrow Chem product, Mumbai, India. Compritol ATO 888 and Precirol ATO 5 were obtained ex-gratia from Gattefosse Corp, France. Dynasan 114 was a gift sample from IOI Oleo GmbH Corp, Germany.

Formulation of sustain release tablets of Theophylline

Granulation by using Iso-propyl alcohol

Drug and lipids were blended for 15 min then granulated by addition of Iso propyl alcohol in sufficient quantity. The moist mass was made to pass through 20# sieve and air dried for 45 min. Dried granules were passed through 25# sieve and thereafter compressed into tablets using single rotary tablet compression machine (Pilot press) using 6mm and 8mm size of dies and punch set (100mg and 125mg tablets were compressed in the size of 6mm dies and punch and 150 mg was compressed in 8mm dies and punch set).

Tablets were formulated by using each lipid in 3 different ratios with respect to the drug. The drug: lipid ratios taken for each lipid were 1:1, 1:1.25, 1:1.5 (Table 1).

Table 1: Formulation composition of sustained release tablets (Theophylline with Novel lipids).

Sr. No.	Formulation Code	Drug: novel lipid ratio	Weight of drug + lipid (g)	Total weight (g)
1	DC1	TP: Comp (1:1)	100 + 100	200
2	DC2	TP: Comp (1:1.25)	100 + 125	225
3	DC3	TP: Comp (1:1.5)	100 + 150	250
4	DC4	TP: Pre (1:1)	100 + 100	200
5	DC5	TP: Pre (1:1.25)	100 + 125	225
6	DC6	TP: Pre (1:1.5)	100 + 150	250
7	DC7	TP: Dyn (1:1)	100 + 100	200
8	DC8	TP: Dyn (1:1.25)	100 + 125	225
9	DC9	TP: Dyn (1:1.5)	100 + 150	250

TP: Theophylline, Comp: Compritol ATO 888, Pre: Precirol ATO 5, Dyn: Dynasan 114.

Drug-Excipient Compatibility studies by Fourier Transform Infra- Red (FTIR) spectroscopy and DSC

Drug and lipids interactions were studied by Fourier Transform Infrared Spectroscopy (FTIR) (PerkinElmer Spectrum Version 10.5.1). The spectra were obtained for the drug and compressed mixture of drug with each of the three novel lipids over a scanning range of 4000-650. The recorded spectrum of drug was compared with the spectra of physical mixture to detect drug-lipid interaction by major shifts in peaks.[20]

Differential scanning calorimetry (DSC)

DSC thermograms of the drug and compressed tablet of binary mixture of drug and lipids were recorded on a TA instrument USA Model-Q10. DSC was done to determine any possible interaction between the drug and lipids. Temperature range of 30-350°C at a heating rate 5°C/min in an atmosphere of nitrogen was used for obtaining DSC graphs. Minor shifts in the endothermic peaks of the drug and lipids mixtures are considered acceptable due to the presence of other components as impurity.

Angle of repose

Funnel method was used for the determination of angle of repose. Accurately weighed granules were taken in a funnel and were allowed to flow freely on to the surface so as to form a conical heap. The funnel's height was so adjusted so that the apex of heap touched the tip of funnel stand. The diameter and the height of the conical heap of powder were recorded and angle of repose was calculated by the following equation.

$$\theta = \tan^{-1}h/r \qquad \text{equation 1.}$$

Where, θ = angle of repose
h = height of heap,
r = radius of the heap base

Bulk density

Both bulk density (BD) and tapped density (TD) were determined by taking a quantity of 10 g. of powder blend from each formula, previously shaken to break any agglomerates formed. This was introduced in to a 100 ml measuring cylinder. The initial volume was recorded and the cylinder was set in bulk density apparatus (PT Ambala Cantt, India) and tapped until no further change in volume seen. BD and TD were calculated by the following equations.

BD = weight of powder blend / untapped volume of packing equation 2.

TD = weight of powder blend / Tapped volume of packing equation 3.

Compressibility Index

Carr's compressibility index was used to measure the compressibility index of the powdered blends. Carr's Index was calculated by using the given equation.

Carr's Index (%) = TD-BD/TD*100 equation 4.

Where, TD = Tapped bulk density
BD = Loose bulk density

Hausner's Ratio

The ratio of bulk volume to tapped volume or tapped density to bulk density was used for the calculation of Hausner's ratio. It was calculated by the following formula.

$$\text{Hausner's Ratio} = V_0/V \qquad \text{equation 5.}$$

Where, V_0 = Bulk volume
V = Tapped Volume

Post compression evaluation

Thickness

Vernier calliper was used for the evaluation of thickness of tablets. Five tablets from each batch were taken and average values were calculated. The tablets were placed between the two arms of vernier callipers for determining the thickness.

Hardness

The hardness of 5 tablets was determined from each formulation by using Monsanto hardness tester. The value was noted in kg and results were expressed as mean ± SD (n = 5).

Friability

Roche friabillator (Swastika, India) was used for checking the friability of tablets. Tablets of a known weight (W_0) were placed in the drum of friabillator at a speed of 25 rpm for 4 min (100 revolutions), dropping the tablets from a distance of 6 inches in each revolution. The tablets were weighed (Wt) again. Percentage friability was calculated from the loss in weight as given in equation. The weight loss should not exceed than 1%.

$$\% \text{ Friability} = W0 - Wt/W0 * 100$$

In-vitro drug release studies of Theophylline matrix tablets

The *in-vitro* dissolution study of Theophylline tablets was conducted by using USP dissolution apparatus (Frontline ΔELTA TP02). Phosphate buffer pH6.8 in

the quantity of 900ml was used as dissolution medium for 12 hr study. Temperature was maintained at 37± 0.5°C. Agitation was provided by rotating the paddle at 75 rpm. At predetermined time intervals 5 ml sample was withdrawn, filtered, suitably diluted and its absorbance was checked at 272 nm by UV Spectrophotometer (Max Electronic, India). Six tablets were (*n=6*) subjected to dissolution studies. The graphs of time vs. % cumulative release were plotted for each batch of formulated tablets.

Kinetics of the drug release

The *in-vitro* drug release data of the selected formulation was subjected to kinetic modelling by fitting the data into different kinetic models like zero order, first order, Higuchi and Korsmeyer-peppas model to establish the drug release mechanism and kinetics. The following equations were used for kinetic modelling.[21,22]

$Q_t = Q_0 + K_0 t$ (Zero order Kinetics) equation 6.

[Where Q_t = drug dissolved in time t,
Q_0 = initial amount of drug in the solution and
K_0 = zero order release constant].[23]

$Q_t = Q_0 + K_1 t/2.303$ (First order Kinetics) equation 7.

[Where Q_t = amount of the drug released in time t,
Q_0 = initial amount of drug in the solution and
K_1 = first order release constant].[24]

$Q_t = K_H t^{1/2}$ (Higuchi model) equation 8.

[Where Q_t = amount of drug released in time t,
K_H = Higuchi dissolution constant].[25]

$Q_t = a + n \log t$ (Korsmeyer-peppas model) equation 9.

[Where Q_t = amount of drug released in time t,
a' = constant incorporating structural and geometric characteristic of the drug dosage form,
n = release exponent].[26]

Statistical analysis used

Statistical analysis was done on *in-vitro* drug release data by using the trial version of the software Graphpad Prism version 8.3.0. The release of drug from the different formulation batches was subjected to ordinary one way ANOVA to check for significant difference in the release at $p<0.05$.

The calculated *p*-value was compared with the tabulated *p*-value to check for significant difference in release on changing the lipid type and lipid ratio. *P*-value less than 0.05 was considered significant.

RESULTS

Compatibility study

Fourier Transform Infrared Spectroscopy (FTIR) was used to study the possible chemical interactions between the drug and the lipids during the preparation of tablets. IR spectroscopic study gave no evidence of interaction between the drug and lipids as can be seen from Figures 1a-1d.

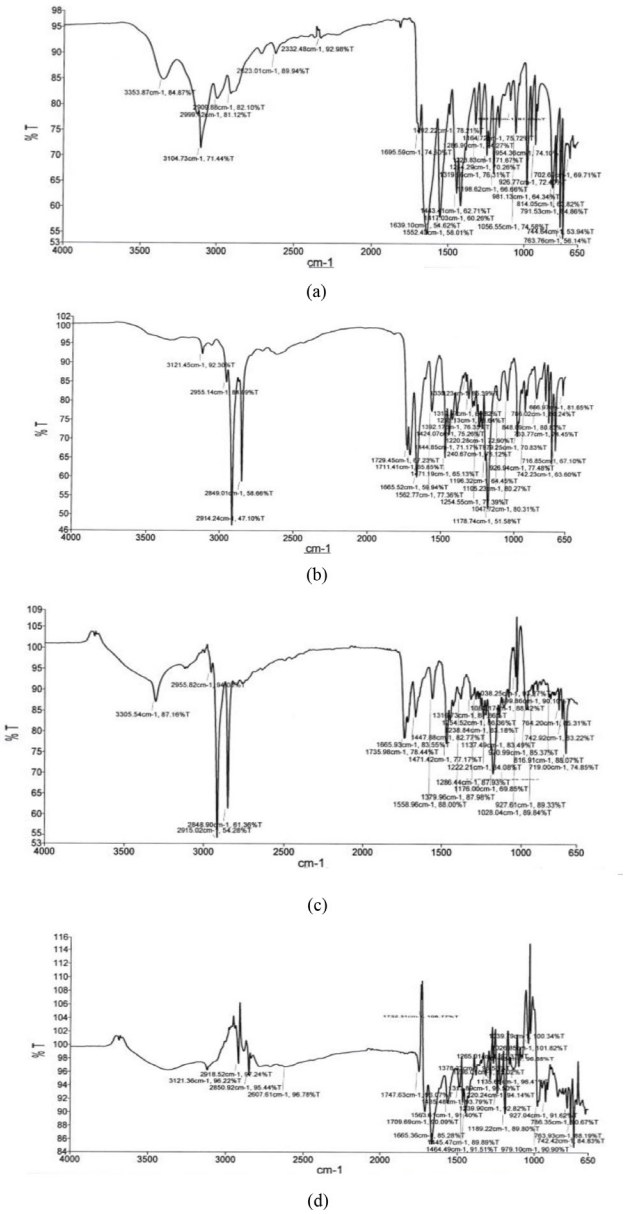

Figure 1: FTIR spectroscopy of (a) Theophylline (b) Theophylline+Compritol ATO 888 (c) Theophylline+Precirol ATO 5 (d) Theophylline+Dynasan 114.

Figure 2 shows thermogram of theophylline and compressed binary mixture of theophylline with lipids compritol ATO 888, precirol ATO 5 and dynasan 114. Thermogram of theophylline shows a sharp peak at 272.6°C representing the point at which it melts as has also been reported in literature.[27] Thermograms of binary compressed mixtures of drug with lipid, compritol ATO 888 [Figure 2(b)], precirol ATO 5 [Figure 2(c)], dynasan 114 [Figure 2(d)] showed endothermic peaks at 262.6°C, 263.8°C and 270.4°C respectively, representing the melting point of the drug. Endothermic peaks at 71.1°C, 55.2°C and 54.5°C in the binary mixture graphs represent the melting point of lipids compritol ATO 888, precirol ATO 5 and dynasan 114 respectively.[28-32] Presence of separate peaks of the drug and lipids in the binary mixture graphs clearly indicates no incompatibility between the drug and the lipids.

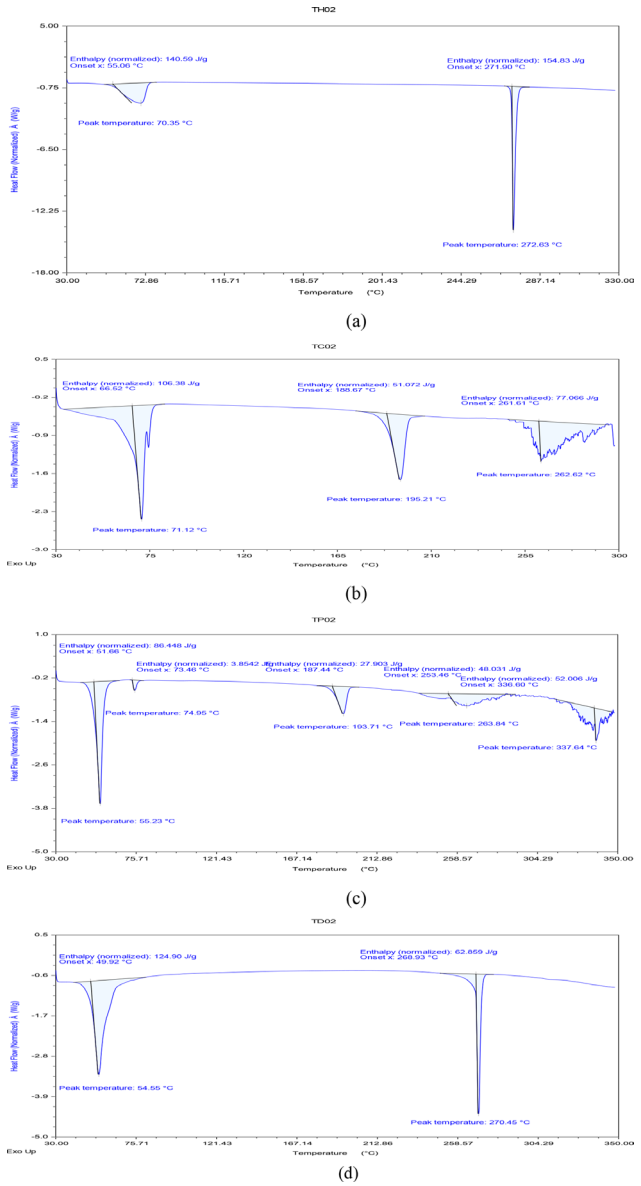

Figure 2: Differential Scanning Calorimetry Graph of (a) Theophylline (b)Theophylline+Compritol ATO 888 (c) Theophylline+Precirol ATO 5 (d) Theophylline+Dynasan 114

Pre compression evaluation

The different micrometrics properties of the granules from each formulation batch have been summarized in Table 2. The granules of various formulation batches containing drug and novel lipid were evaluated for the angle of repose, Bulk Density (BD), Tapped Density (TD), Carr's index, Hausner ratio. The results of pre compression evaluation showed granules of the batches to possess appropriate qualities for compression into tablets. Angle of repose ranged from 25-28° demonstrating adequate flow property in the granules. Carr's index and Hausner's ratio, 12-15% and 0.85-0.87 respectively, established adequate flow of granules. Compressibility index for all formulations were found to be in the range of 12-15%. The values for BD and TD were found to be in the range of 0.46-0.83 g/cm^3 and 0.53-0.96 g/cm^3 indicating good packing capacity.

Post compression evaluation

Tablets of each formulation batch were evaluated for parameters like Thickness, diameter, Hardness and Friability (Table 3). The results of thickness were consistent throughout as can be seen from Table 3. The hardness of tablet was checked by Monsanto hardness tester. The hardness was in range of 5.2±0.1-6.36±0.115kg/cm^2. Friability was found to be 0.67±0.0-0.87±0.01%. All the tablets passed the weight variation test.

Figure 3 Shows the *in-vitro* drug release profile for all the formulated batches and Table 4 shows the percentage drug release for the formulated batches at 1 hr, 6 hr and 12 hr. The results of drug release data can be discussed under two heads, effect of change in type of lipid and effect of change of drug: lipid ratio.

Effect of changing the lipid type

The release data clearly shows that at lower levels of lipids (at 1:1 level) there is a discernible change in release rate on changing the lipid type at all the time points considered (at 1 hr, 6 hr and 12 hr) but as the lipid level in increased to 1.25 and 1.5 the difference becomes smaller and almost insignificant. When the 12th hr data for different lipids was statistically analyzed by ordinary one way-ANOVA at (p<0.05), the results showed significant difference in release for Dynasan1:1, precirol1:1 and Compritol1:1(calculated p<0.0001) but insignificant difference for different lipids when used at 1:1.25 and 1:1.5 ratios as the calculated p=0.3206 for 1:1.25 ratio and p=0.8757 for 1:1.5 ratio (Table 5). From these results Compritol shows the best potential for retarding

Table 2: Evaluation of micrometrics properties of the granules.					
Formulation Code	**Angle of repose***	**BD* (g/cm³)**	**TD* (g/cm³)**	**Carr's index* (%)**	**Hausner's Ratio* (%)**
DC1	26.12±0.05	0.62±0.04	0.71±0.01	12.67±0.02	0.87±0.01
DC2	25.59±0.01	0.58±0.05	0.66±0.01	12.12±0.02	0.88±0.05
DC3	26.06±0.05	0.69±0.01	0.79±0.05	12.65±0.05	0.87±0.01
DC4	27.32±0.02	0.57±0.03	0.66±0.03	13.63±0.03	0.86±0.05
DC5	26.13±0.01	0.46±0.01	0.53±0.05	13.20±0.05	0.86±0.02
DC6	27.08±0.05	0.55±0.05	0.64±0.02	14.06±0.04	0.85±0.04
DC7	25.78±0.01	0.64±0.02	0.73±0.04	12.32±0.03	0.87±0.03
DC8	27.17±0.02	0.83±0.05	0.96±0.02	13.54±0.05	0.86±0.05
DC9	26.25±0.04	0.72±0.01	0.84±0.05	14.28±0.01	0.85±0.02

*Results are expressed as mean ± SD, where n=3. SD: Standard deviation

Table 3: Post compression evaluation of Theophylline tablet.				
Formulation code	**Thickness* (mm)**	**Diameter* (mm)**	**Hardness* (kg/cm2)**	**Friability (%)**
DC1	3.43±0.028	8.13±0.036	5.76±0.057	0.82±0.01
DC2	3.66±0.057	8.23±0.055	6.23±0.115	0.85±0.03
DC3	3.18±0.037	10.06±0.047	5.26±0.057	0.73±0.05
DC4	3.56±0.046	8.13±0.047	6.03±0.057	0.77±0.02
DC5	3.73±0.052	8.16±0.039	6.36±0.115	0.87±0.03
DC6	3.16±0.057	10.1±0.029	5.26±0.057	0.69±0.01
DC7	3.53±0.028	8.16±0.057	6.16±0.057	0.73±0.04
DC8	3.76±0.039	8.26±0.046	6.33±0.057	0.67±0.01
DC9	3.13±0.046	10.13±0.053	5.2±0.18	0.71±0.03

*Results are expressed as mean ± SD, where n=3. SD: Standard deviation

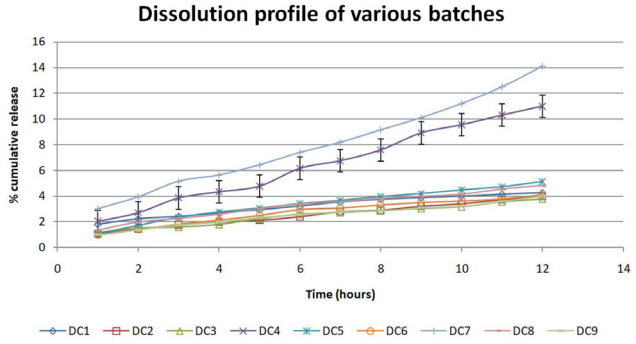

Figure 3: *In-vitro* drug release profile of various formulation batches.

the release of the drug (as it gives the least release at 1 hr, 6 hr and 12 hr).[33,34] Similar results have been reported by Kalakuntta *et al.* in formulating theophylline sustained release tablet using Compritol ATO 888, Precirol ATO 5 and Geleol as lipid and also by Abd-Elbary *et al.* in formulating Etodolac sustained release tablets using different lipids.[35]

Effect of change in drug: lipid ratio

Effect of increasing the lipid ratio can be seen from Table 4 which shows that with lipid having lower Carbon-Chain length of fatty acids, there is a perceptible decrease in release rate at every time point (1 hr, 6 hr and 12 hr), when the lipid part is increased from 1 to 1.25 but for compritol (C_{22}-behenic acid lipid) with the highest number of C-atom in the alkyl chain of its fatty acid, the decrease in release is barely perceptible. For Dynasan and Precirol increase in lipid ratio from 1 to 1.25 provides better matrix cover to decrease drug release rate.[36]

When the lipid ratio is changed from 1.25 to 1.50 insignificant decreases in release rate is observed for all the three lipids at all three observed time points.[37]

When the 12th hr. dissolution data of each lipid was statistically analyzed across its different ratios used i:e 1:1, 1:1.25 and 1:1.5, the results revealed significant difference between the release of Dynasan 1:1, 1:1.25 and 1:1.5 and also for different ratios of Precirol (calculated p<0.0001) but insignificant difference for release from different ratios of Compritol (calculated p=0.8149) as shown in Table 5.

Thus, from the result it can be concluded that the release retardant effect given by the lipid is in the order dynasan< precirol< compritol. Thus, a lipid with greater

Table 4: *In-vitro* drug release data.

Time	1Hr			6 Hr			12 Hr		
Ratio of drug: Lipid % Drug Release*	1:1	1:1.25	1:1.5	1:1	1:1.25	1:1.5	1:1	1:1.25	1:1.5
Dynasan 114	2.785 ± 0.19	1.142 ± 0.12	0.849 ± 0.11	7.390 ± 0.25	3.387 ± 0.06	2.563 ± 0.01	14.14 ± 0.43	4.829 ± 0.07	4.012 ± 0.24
Precirol ATO 5	1.475 ± 0.13	0.969 ± 0.03	0.763 ± 0.06	6.164 ± 0.23	3.410 ± 0.06	2.962 ± 0.45	11.09 ± 0.48	5.126 ± 0.15	4.132 ± 0.27
Compritol ATO 888	1.041 ± 0.03	0.958 ± 0.11	0.932 ± 0.05	3.222 ± 0.05	2.821 ± 0.1	2.597 ± 0.08	4.264 ± 0.02	4.002 ± 0.18	3.780 ± 0.3

*Results are expressed as mean ± SD, where *n*=6. SD: Standard deviation

Table 5: Table showing *P*-values after statistical comparison by ANOVA of different formulation batches.

	Comparison of drug release for different ratios of Dynasan114 at 12th hr	Comparison of drug release for different ratios of Precirol ATO 5 at 12th hr	Comparison of drug release for different ratios of Compritol ATO 888 at 12th hr	Comparison of release for different lipids at 1:1	Comparison of release for different lipids at 1:1.25	Comparison of release for different lipids at 1:1.5
P- value	*P*<0.0001	*P*<0.001	*P*=0.814	*P*<0.001	*P*=0.320	*P*=0.875

Significance level *P*<0.05.

numbe of C-atoms can be used in small amount to give a low release rate for a hydrophilic drug as compared to lipids with less number of C-atoms in the fatty acid. Also, the advantage of increasing the ratio of lipid in the tablet matrix can only be seen upto a certain level above which no benefit is obtained in terms of decrease in the release rate. Thus, batch having 100 mg compritol was selected as it showed good release retardant effect at low level.[38]

The release data of this batch was subjected to kinetic modelling by zero order, first order, Higuchi and Korsmeyer peppas models to determine the mechanism of drug release.

Kinetic modelling of selected batch

Table 6 shows the R^2 and release constants for various kinetic models for release data of batch Compritol 100 mg tablet. It can be seen that highest R^2 (0.967) has been obtained for Higuchi model making it the best fit model for release kinetic and giving evidence for diffusion-controlled release of drug. The value of n=2.8, obtained from Korsmeyer peppes model equation elucidates the mechanism of release of drug to be super case -2 transport.[39]

DISCUSSION

The results of drug-excipient compatibility study conducted by FTIR and DSC showed no interactions between the drug and the lipids used as the FTIR and DSC graphs showed no major changes in the position of peaks obtained. Minor shifts in the peaks are considered acceptable as the presence of excipients acts as an impurity for the drug.

The angle of repose characterizes internal friction or cohesion of the particles. A high value of angle of repose shows the powder to be cohesive and a low value indicates a non-cohesive powder. The values (Table 2) for angle of repose (< 30) indicated good flow properties of granules and this was further supported by low Carr's compressibility (12-14.5%) index and Hausner ratio values (less than 0.89). Particle size distribution, particle shape and the tendency of particle to adhere together determines the bulk density of the powder. The results obtained for bulk and tapped density suggested good packing capacity of the granules prepared.

Very little variation in thickness of tablets of each formulation batch suggests consistency in particle size of the granules giving uniform behavior during compression. The hardness of all the batches of tablets

Table 6: Kinetic modelling of release data of DC1 batch.

Formulation Name	Zero Order		First Order		Higuchi		Korsmeyer Peppes	
DC1	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_P
R^2 and release constant	0.7986	0.4426	0.8194	0.0960	0.9676	1.252	0.7404	1.0043
							n = 2.8	

was within the desired range. Adequate hardness is desired to maintain integrity of tablet during handling.

The release data clearly shows that at lower levels of lipids (at 1:1 level) there is a discernible change in release rate on changing the lipids type at all the time points considered (at 1 hr, 6 hr and 12 hr) as is also evident from the results of statistical analysis given above but as the lipid level is increased to 1.25 and 1.5 the difference in release becomes smaller and almost insignificant (calculated p value greater than 0.05 for both ratios)for different lipid types. The probable reason for this effect could be that at higher lipids levels the drug gets completely surrounded by the lipids and so the individual hydrophobicity of the lipid becomes less important in controlling the release whereas at lower levels the individual hydrophobicity of the lipids play a role in controlling the release. At lower levels (1:1) it can be seen at all three selected time points for the composition, Compritol shows the best potential for retarding the release of the drug (as it gives the least release at 1 hr, 6 hr and 12 hr) indicating its higher hydrophobicity as is evident from the number of carbon atom in its fatty acid chains (C_{22}) as compared to Dynasan 114 (C_{14}) and Precirol (C_{16}/C_{18}). It has been shown that as the alkyl chain length of fatty acid increase the hydrophobicity of resulting lipid also increases as has also been reported by Li *et al*. and Sudha *et al*.[40,41]

Effect of increasing the lipid ratio can be seen from Table 4 which shows that with lipid having lower Carbon-Chain length of fatty acids there is a perceptible decrease in release rate at every time point (1 hr, 6 hr and 12 hr), when the lipid part is increased from 1 to 1.25 but for compritol (C_{22}-behenic acid lipid) with the highest number of C-atom in the alkyl chain of its fatty acid, the decrease in release is barely perceptible. The reason behind this trend is probably that compritol because of its higher chain length of fatty acid provides sufficient hydrophobicity at lower levels to minimize water permeation, wetting and dissolving of drug particle and then diffusion and any further increase in the lipid ratio does not provide any significant benefit in terms of decrease in release rate. But for dynasan and precirol increase in lipid ratio from 1-1.25 provides better matrix cover to decrease drug release rate.[42,43]

When the lipid ratio is changed from 1.25 to 1.50, insignificant decrease in release rate (as compared to 1:1 ratio) is observed for all the three lipids at all three observed time point probably because the matrix gets saturated with lipid at 1.25 level providing maximum coverage to drug particles and minimizing water permeation and drug diffusion and thus giving no further benefit in increasing the lipid ratio to 1.5 as has also been reported by Quadir *et al*.[44]

Thus, from the result it can be concluded that the release retardant effect given by the lipid is in the order dynasan< precirol< compritol. It can also be interpreted that as the number of C-atoms in the alkyl chain of the fatty acid of lipid increases, its hydrophobicity increases potentiating its release retardant property and minimizing its amount in forming the release retarding matrix.[45] These results are analogous with result of Abd-Elbary *et al*. who had formulated lipid matrix tablet of Etodolac using sodium stearate as lipid matrix former.

Thus, a lipid with greater number of C-atoms can be used in small amount to give a low release rate for a hydrophilic drug as compared to lipids with less no of C-atoms in the fatty acid. Also, the advantage of increasing the ratio increased of lipid in the tablet matrix can only be seen upto a certain level above which no benefit is obtained in terms of decreasing the release rate. Thus, batch having 100 mg compritol was selected as it showed good release retardant effect at low level of lipid.[46]

The release data of this batch when subjected to kinetic modelling showed the release to be dominated by Higuchi model (R^2=0.9676) suggesting diffusion controlled release as it is a lipid matrix tablet. The value of n=2.8, obtained from Korsmeyer peppas equation elucidates

The mechanism of release of drug to be super case-2 transport which is characterized by relaxation of polymer.[47]

CONCLUSION

The study was carried out with the objective of comparing the release retardant effect of the three novel lipids (Compritol ATO 888, Precirol ATO and

Dynasan 114) by preparing sustained release tablets of highly water-soluble drug (Theophylline). The mixture of theophylline and three novel lipids were compressed by direct compression method. Drug and novel lipids interaction was determine by FTIR spectroscopy and DSC. The drug release from the sustained release tablet was studied using USP-Ⅱ dissolution apparatus and other evaluation parameters were found to be within acceptable range. The release was analysed to determine the lipids showing the best retardant effect. The study showed that Compritol ATO 888 was more hydrophobic, as it has more numbers of Carbon-atoms in its fatty acid chain, as compared to Precirol ATO 5 and Dynasan 114 and demonstrated most effective release retardant effect.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

BCS: Bio pharmaceutics Classification System; **FT-IR:** Fourier Transform Infra-Red; **DSC:** Differential scanning calorimetry; **USP:** United State Pharmacopoeia; **mg:** Milligram; **BD:** Bulk Density; **TD:** Tapped Density; **%:** Percentage; °C: Degree Centigrade; **UV:** Ultra-Violet; **rpm:** Revolution Per Minute; **µg/mL:** Microgram/Millilitre; **SD:** Standard Deviation;

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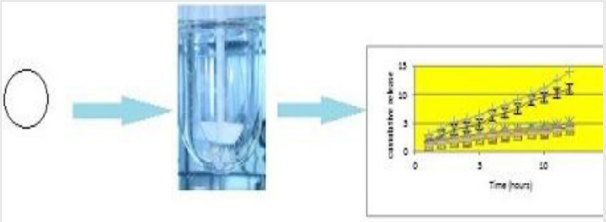
PICTORIAL ABSTRACT



Pictorial representation of release retardant effect of lipids on formulated tablets.

About Authors

Shweta Agarwal is an Associate Professor, Deapartment of Pharmaceutics, L.R Institute of Pharmacy, Solan. She has 15 years of teaching and research experience and has published more than 30 review and research articles in peer reviewed journals. she has reviewed papers for several reputedInternational journals and has mentored 20 post-graduate students. Her areas of interest include mucoadhesive systems, colidal drug delivery and topical gels.

SUMMARY

In the present study the release retardant effect of 3 novel lipids, Compritol ATO 888, Precirol ATO5 and Dynasan 114 was compared by using BCS class I drug, Theophylline, as the model drug. Drug-excipient compatibility was checked by FTIR and DSC, showing the drug to be compatible with the lipids used. Sustained release tablets of theophylline were formulated taking the 3 lipids in different ratios (1:1, 1:1.25 and 1:1.5) with respect to the drug. All the 9 prepared batches of tablets were subjected to *in-vitro* drug release study, using USP type-II apparatus. From the drug release data obtained, DC1 batch having 100mg drug and 100mg Compritol showed optimum, desirable release rate and was selected for further studies. Release data of DC1 batch was used for kinetic modeling. The release showed to be following Higuchi model (R^2= 0.967) and release mechanism was found to be super case 2 transport (n=2.8) from Korsmeyer-Peppas model. The results of the study showed the release retardant potential of the lipids to be in the order Dynasan< Precirol< Compritol, establishing Compritol as the best release retardant lipids from the 3 lipids used. Compritol possessed superior potential for retarding the release of drug probably because of greater number of Carbon atoms (C22) in its fatty acid chain, making it more hydrophobic than other lipids studied.

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