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Original Article

Sustained Release Multiparticulates via Powder Coating

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Abstract

Hydrophobic grade fumed silicas are generally used in tabletting as lubricants. They are also found to retard the release of pharmaceutical actives. This is because of their hydrophobic nature, which gives good cohesive and adhesive properties. considering this point it was thought that they could be used as dry coating agents for solid dosages forms. The model drug selected for this work was paracetamol in granular form and the various coating materials evaluated were hydrophobic grade fumed silicas such as Wacker HDK H-20, Wacker HDK H-15 and Aerosil R-972. Aerosil R-972 was found to be satisfactory and extended the release process up to 8 h at concentrations as low as 0.75%. Key parameters such as coating, mixing duration, rotation speed in dissolution test, and medium composition were studied, which were shown not to alter the release significantly.

Keywords: Hydrophobic fumed silica; Aerosil R-972; SR coating; Powder coating.

Introduction

In recent years considerable attention has been focused on the development of new drug delivery systems. These are capable of controlling the rate of drug delivery or sustaining the duration of therapeutic activity. Significant advances in sustained or controlled drug delivery have been made in the last few decades (1). Coating with polymers or other suitable materials is one way to make the product sustained-release. This is divided into 1) Sugar Coating, 2) Film Coating, 3) Compression Coating and 4) Micro-Encapsulation.

Most of the methods involve various types of coating using liquid application. The major disadvantages of these methods are, being time consuming, involving many steps, being expensive and apart from cracking and chipping sometimes also show problems like lamination, orange peel or roughness of the coat. The question is that, whether it is possible to use a dry coating method, which would be simple, economical, safe and free from complex operation (2). Literature survey shows that certain hydrophobic tablet lubricants, e.g. magnesium stearate, have been found to retard the dissolution of salicylic acid from model compressed tablets while water soluble surface active agents such as sodium lauryl sulfate enhanced markedly the dissolution rate markedly (3).

The work of Strickand suggests that when lubricants are added to a tablet granulation, they form coat around individual granules, which remain more or less intact during the process of tablet compression. Interference by these agents with the dissolution of drugs is therefore a likely fact (4). Valerie states that the most common method for ensuring adequate lubrication at the interface between powders and metallic surfaces during tablet and capsule

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manufacturing is the addition of lubricants stearic acid and magnesium stearate as fine powders. These materials being hydrophobic in nature inhibit the penetration of all aqueous fluids into the final product. This limitation of access results in retardation of dissolution of tablets and capsules (5).

To the conventional methodologies of coating a relatively new process, i.e. the use of hydrophobic powders as coating materials, has been added. This process is also known as dry coating method (6). Hersey first reported about this type of coating and suggested a new term for it as "Ordered Mixing". He defined this as mixing of a fine cohesive powder and a coarser free flowing powder, where the fine particles get attached to the surface of coarse particles. Such mixing may lead to formation of sufficiently cohesive/adhesive structure with dissimilar particles demonstrating the desired release retardation (7).

The objective of this work was to develop a coating process that is not only simple but also economical and less time-consuming using the concept of ordered mixing using various grades of hydrophobic fumed silica. The advantages of using hydrophobic fumed silica are being: (a) composed of extremely minute particles, thus possessing very large specific surface area and excellent dry powder coating characteristics (b) economical (c) non-hazardous (8). Another objective of this work was to study whether the coating process is affected by mixing time and speed and dissolution medium and the speed of mixing of dissolution medium.

Experimental

Materials

In this study paracetamol was used as a model drug as many researchers have used it for its easy estimation (9), which was obtained from Research Lab. India. The coating materials tested were Wacker HDK H-20 (Wacker Metroark Mumbai, India) and Wacker HDK H-15 (Wacker Chemie GmbH, Germany) and Aerosil R-972 (Degussa-Huls Corporation Mumbai, India). Hard gelatins capsule were gifted (Associated Capsules, Mumbai, India).

Table 1. Consolidated table of formulae and treatment.

Ingredients	Batch no.		
	B1	B2	B3
Paracetamol	+	+	+
Aerosil R-972	-	-	+
Wacker HDK H-15	-	+	-
Wacker HDK H-20	+	-	-

Methods

Preparation of coarser core particles

Preparation of SR multiparticulate systems

Paracetamol powder was turned into the coarser particles by crystallization followed by size separation and selection. Paracetamol was dissolved in water kept at 80°C, filtered and rapidly cooled under stirring. Crystals were classified according to their sizes by being passed through 100 # mesh wire screens.

Method of dry coating

Extended release paracetamol capsules were prepared through preparation of the coarser paracetamol core material by crystallization. Dry coating of the coarser core material was performed by using very fine (passed through 150# mesh sieve) hydrophobic fumed silica. These coated cores were filled into the hard gelatin capsules. The batch details are described in Table 1.

The coarser core materials were coated in a cube mixer (Lab Scale Cube Mixer: Erweka, Germany) with the coating material i.e. hydrophobic grade fumed silica. The batch size for this step was 50 g. The coated materials were then filled into hard gelatin capsules. Coat: Core ratio, mixing speed and mixing duration were also studied.

In vitro dissolution

Release of paracetamol from these formulations was investigated using USP Dissolution Apparatus 1 (Electro Lab, India). Distilled water, 0.1 N HCL (pH=1.2) Buffer (pH=7.8), and surfactant solution (0.1% Tween 80) were used as media. 10 ml samples were withdrawn after various time intervals untill 8 h and filtered through membrane filters. An equivalent volume of fresh dissolution medium was immediately added into dissolution vessel

Table 2. Comparison of $t_{50\%}$ and DE (%) values for different batches.

Batch no.	DE (%)					$t_{50\%}$ in h
	1 h	2 h	3 h	6 h	7 h	
B1	44.67	60.66	70.97	-	-	0.33
B2	34.59	48.71	57.73	-	-	0.63
B3	5.28	10.31	15.37	31.47	37.13	4.80

after each sample was withdrawn. Contents of paracetamol were determined by measuring the absorbance at 249 nm by using a UV-V is spectrophotometer (Jasco, Japan). Various mathematical models were applied to study the behaviour of drug release.

Statistical studies

The statistical study used in the entire work was paired student t test and were calculated using the "GraphPad Instat®" version 3.06. Software.

Results and Discussion

Choice of coating material

Since dry coating is nothing but blending of the core and coat material, in the present work the search for the coat started with various hydrophobic materials like magnesium stearate and stearic acid. However, due to their poor attachment to the core material indicated by the dissolution studies, these materials were rejected. Hydrophobic fumed silicon dioxide not only is hydrophobic in nature, but also due to its very fine size it gets well attached over the coarser core material. Keeping this in mind, three different grades of hydrophobic fumed silica viz. Wacker HDK H-20, Wacker HDK H-15 and Aerosil R-972 were studied. Initially the experimentation started with H-20, but due to inadequate release retardation we shifted to more hydrophobic grade H-15, and subsequently to Aerosil R-972 which was found to be the best material for this work. This material could retard and prolong the release up to 8 h, which is shown in Figure 1. The $t_{50\%}$ and dissolution efficiency (DE) values are included in Table 2. It can be seen that the $t_{50\%}$ values increased from 0.33 h and 0.42 h for Wacker HDK H-20, Wacker HDK H-15 respectively to 4.8 h for Aerosil R-972 coated paracetamol cores. The value of DE at 3 h for Wacker HDK H-20 was 70.97%, for Wacker HDK H-15 was 57.73% and for Aerosil R-972 it was 15.37%. The DE values decreased in the order of Wacker HDK H-20>Wacker HDK H-15>Aerosil R-972 The values indicate that Aerosil caused maximum release retardation in comparison with both the Wacker HDKs. Coating attempted in the earlier part of the work (Wacker HDK H-20), had not retarded the release up to the desired 7-8 h. Contrary to, Wacker HDK H-20, Wacker HDK-15 could show good retardation,although the concentration required was more than 5%. The phenomenon can be explained by the more hydrophilic nature of Wacker HDK H-20 in comparison to Wacker HDK H-15. The surface area of hydrophilic content of Wacker HDK H-20 is 170-230 m^2/g while that of Wacker HDK H-15 is 110-130 m^2/g. But the silane content is higher in Wacker HDK H-15 as compared to Wacker HDK H-20. Thus, Wacker HDK H-20 allowed more penetration of dissolution medium in comparison to Wacker HDK H-15 (12). Aerosil R-972 retarded the release of paracetamol up to 8 h in a much less concentration, i.e. as low as 0.75%. It was observed that among various grades of hydrophobic fumed silica studied for release retardation, Aerosil R-972 decreased the

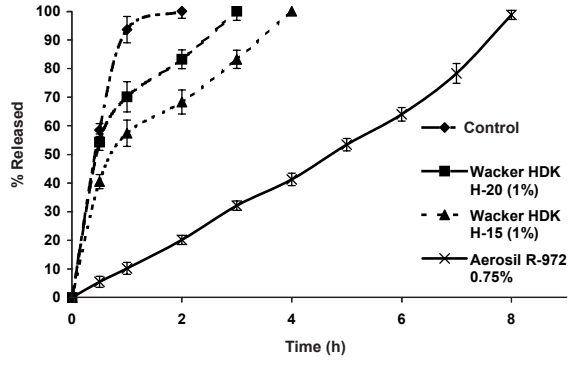

Figure 1. *In vitro* release of paracetamol from granules coated with different grades of hydrophobic fumed silica.

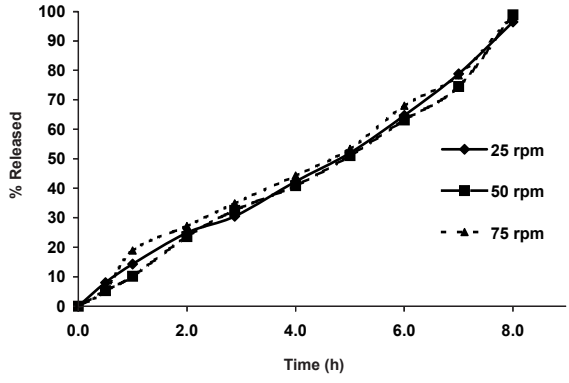

Figure 2. *In vitro* release of paracetamol from granules coated with 0.75% Aerosil R-972 using different mixing speeds.

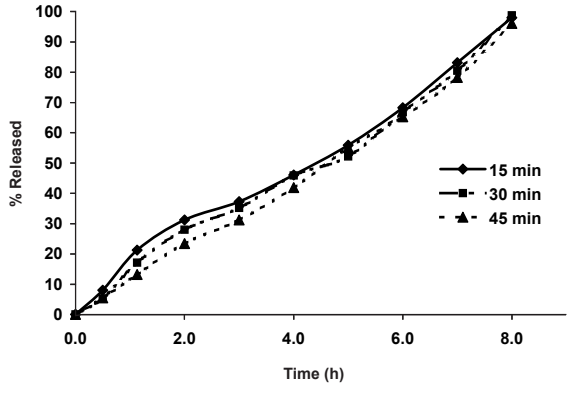

Figure 3. *In vitro* release of paracetamol from granules coated with 0.75% Aerosil R-972 using different mixing times.

release rate significantly ($p < 0.05$). Aerosil R-972 is prepared by a more hydrophobic cross-linking technique as compared to Wacker (8). Thus, it is able to sustain the release of the drug in a more effective way as in comparison to the other fumed silica tested. Parameters studied during this study were Aerosil R-972 concentration, mixing speed, and mixing time Keeping Aerosil R-972 concentration constant (0.75%), the other parameters were varied.

Effect of ordered mixing condition

Dry coated mixtures may be prepared by simple mixing. The mixing was carried out in a cubic mixer. The parameters studied were mixing speed and mixing time.

Mixing speed

The batch B3 was tested to study the effect of various mixing speeds on drug release as it was able to give a more sustained release than any other fumed silica tested. Figure 2 shows that the mixing speed varied between 25 to 75 rpm, did not show any significant difference ($p > 0.05$). The study was important, as at lower speeds mixing was inadequate while at high speeds, some de-mixing might occure. Appropriate conditions of mixing are needed for proper adherence of the coating material. But in this case all the three speeds tested were adequate to give an ideal adherence without any de-mixing.

Mixing duration

To optimise the duration of mixing, batch B3 were mixed at 50 rpm for 15 to 45 min. The Aerosil R-972 exhibited very good adhesive properties, and within a period as short as 30 min it showed desired attachment over the core particles, which can be seen in Figure 3. The mixing time was found to have no remarkable ($p < 0.05$) effect in the coating, indicating the unique cohesive and adhesive qualities of Aerosil R-972, which is in accordance to the literature (7). The optimum mixing time was determined to ensure that there was no unnecessary and excessive mixing while reaching to an adequate smooth extension of the release.

Thus, for the further studies mixing time and speed was set to 15 min and 50 rpm respectively.

Effect of dissolution condition

pH

Figure 4 shows the dissolution profile of capsules containing dry coated paracetamol cores with 0.75% Aerosil R-972 in three dissolution media. The three different dissolution media selected were. Distilled water, acidic medium ($pH = 1.2$), and slightly alkaline phosphate buffer ($pH = 7.8$). The graph indicates that there is no significant difference ($p > 0.05$) between pH of 1.2, pH of 7.8, distilled water. This can be related to two things: Firstly, the polymer being hydrophobic, does not easily allow the penetration of medium into the coated core; Secondly, the drug does not show pH dependent solubility. The release profile was not affected by the pH of the dissolution medium nor the surfactants. The effect of surfactants on the dissolution profile of the paracetamol is

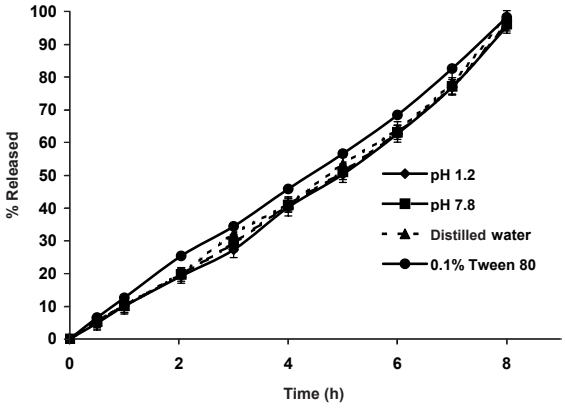

Figure 4. *In vitro* release of paracetamol from granules coated with 0.75% Aerosil R-972 in different dissolution media.

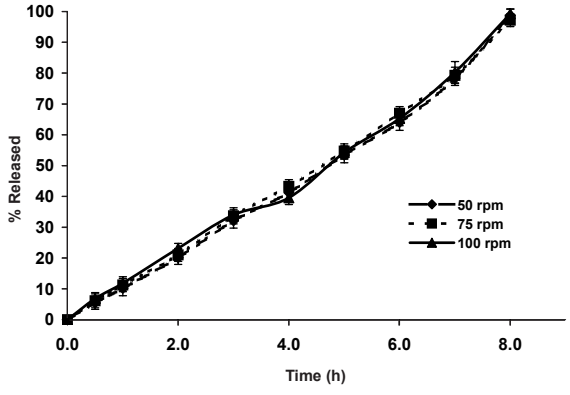

Figure 5. *In vitro* release of paracetamol from granules coated with 0.75% Aerosil R-972 at different dissolution mixing speeds.

discussed further.

Stirring speed

ure 5 shows the dissolution profiles at stirring speeds of 50, 75 and 100 rpm using USP-1 apparatus. The results indicated no significant difference ($p>0.05$) in drug release when coated with Aerosil R-972. Thus, it could be stated that the adhesive force between fine Aerosil R-972 and the coarser drug particles is high enough to not being affected at higher dissolution speeds, which is in accordance to the literature (7). Therefore, there is every chance that the drug will release in the same manner *in vivo,* as it has shown *in vitro*.

Thus, it was decided to continue the dissolution in distilled water and at 100 rpm.

Surfactant

As our GIT contains surfactants, it was decided to carry out a drug release study with the use of a surfactant. The release profile is shown in Figure 4. It was noted that Tween 80 in a concentration as high as 0.1% did not damage the profile. The f_2 values were calculated for the dissolution without tween 80 and the one performed in distilled water. A value of 66.29 was obtained which indicated that the two release profiles were similar. There was a slight increase in release rate from 11.415 to 11.831%/h for dissolution in distilled vs. water 0.1% tween 80 solution. This proved the strength of attachment of the coat on the core. Being powder coating and not a typical film, coating it might be washed off by the surface active GIT fluids, nullifying the drug release extension. So carrying out this study was necessary.

The possible reason for release extension is the hydrophobic nature of Aerosil, which retards penetration of dissolution medium. However, due to the effect of hydrodynamics in the dissolution medium and fluid composition, some erosion of the coat or pore formation on coat takes place. This leads to a limited entry of dissolution medium into the core. The medium causes dissolution of the drug (paracetamol here) creating a flux.

Kinetic treatment

Different kinetic treatments such as first order, zero order, Higuchi and Korsemeyer-Peppas models were applied and correlation coefficients were calculated awhich are shown in Table 3. The kinetic data hints that the release of the drug was by diffusion. Thus, to determine the type of diffusion, Korsemeyer-Peppas model was applied (13, 14). In general, drug release follows a Fickian mechanism, but some-times because

Table 3. Kinetic assessment of release data for batch B2.

Treatment	r^2	n	k
First	0.6216	-	-
Zero	0.9970	-	-
Higuchi	0.9770	-	-
Korsemeyer Peppas model	0.9965	1.033	0.0112

k is release rate constant; n is diffusional release exponent; r^2 is correlation coefficient.

of the presence of other additives, a mixture of diffusion (Case I) and chain relaxation (Case II) is seen. However, when drug diffusion does not follow a Fickian mechanism, it is very similar to a zero-order continuous and homogeneous release kinetic. Dissolution of paracetamol from the coated cores showed anomalous behaviour as 'n' values were above 1. The low value of 'k' indicated that there was a initially burst release (15).

Conclusion

Based on the results, it could be concluded that hydrophobic fumed silicas satisfactorily decreased the drug release rate from paracetamol granules. Among all the grades used in this experimentation, Aerosil R-972 was found to be the best, at a very low concentration of 0.75%. This caused a release extension up to 8 h.

The granules were found to be remaining intact even after 8 h. As hinted by the release kinetics it could be concluded that the release process may occure by diffusion and the mechanism of diffusion is anomalous. Therefore, a simple coating method has been suggested to prepare oral SR multiparticulates exhibiting smooth release of the drug, and being minimally affected by the dissolution media and speed and the presence of surfactants.

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