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Effect of sintering on controlled release profile of diltiazem hydrochloride tablets prepared by melt granulation technique

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Abstract

The study was designed to formulate and evaluate diltiazem hydrochloride wax matrix tablets for controlled release using sintering technique. Granules of diltiazem hydrochloride-wax were prepared by melt granulation technique. This was formed by triturating the drug powder with a melted carnauba wax (drug: wax ratio, 4.5:1). Matrix tablets of diltiazem hydrochloride-wax were prepared by compressing the drug-wax granules at constant pressure. The tablets were subsequently sintered at 60 and 70^{o}C for 1, 3 and 5h. The unsintered, sintered and commercial brand (CB) of sustained release tablets of diltiazem hydrochloride were evaluated for tablet hardness, friability and *in vitro* dissolution rate. Release kinetics and mechanism were confirmed by measuring the correlation coefficient (r-values) of the release data. The optimized formulation was characterized with Fourier-Transform Infrared (FTIR) spectroscopy to investigate any drug-excipient interaction. Generally, sintered tablets had a higher hydrophobicity than the unsintered tablets. Controlled release of diltiazem hydrochloride-wax matrix tablets from the sintered tablets depended on the temperature and time of sintering. For instance, tablet formulation sintered at 60 and 70°C for a period of 3h gave maximum release (m_{∞}), time to attain maximum release (t_{∞}) and dissolution rate (m_{∞}/t_{∞}) of 94%, 91.2%, 6h, 12h, 15.7%h^{-1} and 7.6%h^{-1} respectively. Results showed that cumulative percent of drug released from the optimised formulation was comparable to that of CB. There was no chemical interaction between the drug and excipients before and after sintering. This indicates that sintering technique can be used to increase the hydrophobicity of formulations and hence increase drug retardation.

Keywords: Sintering; Diltiazem hydrochloride, Melt granulation, Controlled release; Carnuba wax.

INTRODUCTION

Controlled release dosage forms have made significant progress in terms of clinical efficacy and patient compliance (Merkus, 1986). Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact by the application of heat (Rakesh and Ashok, 2009). Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering (Satyabrata *et al.*, 2010). The development of oral

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controlled release dosage formulation of metformin hydrochloride matrix tablets by sintering the polymer matrix with organic vapour such as acetone has also been investigated (Flowerlet *et al.*, 2010). The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of drug release from dosage forms (Cohen *et al*., 1984). Recently, Satyabrata *et al* (2010) designed a mucoadhesive buccal tablets of Perindopril, an antihypertensive drug by sintering technique. In the study, the applicability of thermal sintering technique in the development of mucoadhesive buccal tablets showed that the release rate of the drug decreased with increase in sintering time. Hence, the results showed the suitability of thermal sintering technique in the development of mucoadhesive buccal tablets for the controlled release of Perindopril. The process of sintering affects the pore structure and strength of plastic matrix tablets (Rowe *et al*., 1973).

On the other hand, melt granulation is a technique whereby the drug powder is triturated with a melted wax serving as a hydrophobic control release agent (Uhumwangho and Okor, 2006). The advantage of this technique is that it is simple and does not require the use of organic solvent which is hazardous to the environment.

Diltiazem hydrochloride is a non-dihydropyridine member of the group of drugs known as benzothiazepines, which are a class of calcium channel blockers. It is used in the treatment of hypertension, angina pectoris, and some types of arrhythmia (Buckley *et al*., 1990). The bioavailability of diltiazem hydrochloride is about 30% to 40% due to first pass metabolism (Hermann *et al.*, 1983; Smith *et al*., 1983). Its biological half-life is about 3.5 hours. Hence, it requires multiple daily drug dosage to maintain adequate plasma concentrations. However, the high solubility of diltiazem hydrochloride is a major challenge in designing its controlled drug delivery system (CDDS). Thus, it is a suitable model drug for CDDS. The extreme release retarding ability of carnuba wax followed by different sintering conditions (i.e. temperature and time) may be utilized to design a CDDS of diltiazem hydrochloride.

EXPERIMENTAL

Materials. The active ingredient used in the study was diltiazem hydrochloride (Cipla Ltd, Goa, India). The matrix materials used were carnuaba wax (SD Fine Chemicals, Mumbai, India), a fine yellow waxy solid with melting point of 82-88^{o}C. Magnesium stearate (Qualikems Fine Chemical Pvt Ltd, India) was used as the lubricant. Other materials used were analytical grade. A commercial brand (CB) of sustained release formulation of diltiazem hydrochloride was purchased from the market. The manufacturing, expiring dates and batch number were recorded.

Melt granulation technique. Carnuaba wax (20 g) was melted in a stainless steel container in a water bath at a temperature higher than its melting point (i.e. 90^{o}C). A sample of diltiazem powder (90 g) was added to the melted wax and thoroughly mixed with a glass rod. It was then allowed to cool to room temperature (35 ± 2^{o}C). The mass was pressed through a sieve of mesh 10 (aperture size; 710 μm) to produce wax-matrix granules.

Tableting. The matrix granules were compressed into tablets using a rotary compression machine (Model Riddhi, Ahmedabad, India) to form flat faced tablets with a diameter of 6mm. The weights of the tablets were 111mg. The drug contents for the controlled release was 90mg, magnesium stearate (0.9% w/w) was added to the granules prior to compression. Sufficient pressure was applied to keep the hardness at 5.5±0.02 kg/cm^{2}. The tablets were allowed to

equilibrate in a desiccator for 24 h before their evaluation.

Sintering of tablets. The tablets from each batch were then subjected to thermal treatment by placing on aluminum foil and subjecting to sintering at different temperatures (Kondaiah 2002; Luk and Jane, 1996) i.e. 60 and 70^{o}C for different durations (1, 3 and 5h) in a hot air oven (Labhosp, Mumbia, India).

Determination of tablet hardness. The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester (Brook and Marshall, 1968). The mean value of the fracture loads was recorded. The determination was carried out in triplicate, using different batches of tablets and mean results reported.

Friability test. The friability test is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Five tablets were placed in the drum of an Erweka friabulator (Heusenstamm, Germany) rotating at 20 rev per min for 10 min. The percentage dust formed due to the impact was determined and taken as index of friability. The test was carried out in triplicate.

***In vitro* dissolution test.** One tablet from each batch of the formulation or the CB was immersed in 900ml of leaching fluid (0.1N HCl) and maintained at 37±2^{o}C. The fluid was stirred at 100rpm (Model Disso 2000, Lab India). Samples of the leaching fluid (5ml) were withdrawn at selected time intervals with a syringe fitted with a cotton wool plug and replaced with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and analysed for content of diltiazem hydrochloride spectrophotometrically at λ_{max}, 236nm using an Elico SL 210 UV-Visible double beam spectrophotometer (Elico, India). The amount released was expressed as a percentage of the drug content in each dissolution medium. The dissolution test was carried out in triplicate and the mean results reported.

Statistical analysis. All data obtained were subjected to student t- test ($p < 0.05$) to test for significance of difference.

Determination of rate order kinetics. The dissolution data were analyzed on the basis of zero order, (cumulative amount of drug released vs. time), first order rate (log cumulative amount of drug remaining vs. time), Higuchi model (cumulative amount of drug released vs. square root of time) and Korsmeyer and Peppas (log cumulative amount released vs time). These are the most frequently reported kinetics of drug release from drug particles and their solid dosage forms (Higuchi, 1963; Korsmeyer *et al*., 1983; Peppas, 1985; Harland *et al*., 1988).
The kinetic models order equations are:

Zero order: $m = k_0 t$ (1)
First order: $\log m_1 = \log m_0 - 0.43\, k_1 t$ (2)
Higuchi: $m = k_H t^{1/2}$ (3)
Korsmeyer and Peppas dissolution model
$\log \%m = \log k_2 + n \log t$ (4)

where m is the percentage (%) amount of drug released in time t; m_1 is the residual amount (%) of drug in time t; m_0 is the initial amount of drug (100%) at the beginning of the first order release; k_0, k_1, k_H and k_2 are the release rate constants for the zero, first order, the Higuchi models and Korsmeyer and Peppas dissolution models respectively. The n is the diffusional release exponent that could be used to characterize the different release mechanism. For a tablet having cylindrical shape, n value below 0.45 indicates Fickian diffusion and n value between 0.45 and 0.89 indicates anomalous transport, often termed as first-order release. If the n value reaches 0.89 or above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the drug is released by zero-order mechanism. In this case, the drug release is dominated by the erosion and swelling of the polymer (Ritger

and Peppas, 1987). The correlation coefficient (r) for each rate order was also calculated. The dissolution profile was considered to follow a particular rate order if the r value was ≥ 0.95 (Uhumwangho and Okor, 2006).

Fourier Transform Infrared (FTIR): The FTIR spectrum of the different samples were recorded in an Infrared spectrometer (Nicolet Magna 4R 560, MN, USA) using potassium bromide discs prepared from powdered samples.

RESULTS AND DISCUSSION

Effect of sintering on tablet hardness: The effect of sintering temperature and time on tableting physical parameters is presented in Table 1. It was observed that the tablet hardness increased as the sintering temperature and duration of sintering increased. For instance, at 1h and 3h sintering time with a temperature of 60^{o}C the tablet hardness were 5.5 and 5.7kg/cm^2 respectively. There was no statistically significant differences ($p>0.05$) in their hardness values. On the other hand, for a sintering time of 3h with temperatures of 60 and 70^{o}C the hardness values were 5.7 and 7.8kg/cm^2 respectively. There was a statistically significant difference in their hardness values ($p<0.05$). This indicated that increase in temperature as well as duration of sintering affected the hardness of the tablets formulation. The hardness value of the CB was 5.9±0.2kg/cm$^{2.}$ The friability values for all the formulations were < 0.53% (Table 1).

Dissolution profiles of tablets. The dissolution profiles of the CB, unsintered and sintered tablets at 60^{0}C at different time durations are presented in Fig 1. It was observed that the unsintered tablets were unable to retard the release of the drug for 12h. The sintered tablet retarded the drug release as the duration of sintering increased. For instance, when tablets was sintered at 60^{o}C for durations of 3h and 5h the maximum release (m_∞) and time to attain maximum release (t_∞) were 94%, 96%, 6h and 8h respectively (See table 2). The sintering time markedly affected the drug release properties of the carnauba wax matrices tablets. The release of diltiazem for batches CW5 to CW7 after sintering at 70^{o}C for different time duration is showed in Fig 2. It was observed that the sintered tablets at 70^{o}C were able to retard the drug for 12h. For instance, at 70^{o}C for 3h and 5h, the m_∞ and t_∞ were (94.2 %, 89.5 %) and (12h, 12h) respectively (See Table 2). The dissolution rate (m_∞/t_∞) of all the formulations is shown in table 2. The dissolution rate also decreased as the sintering temperature and time increased (Table 2). Generally, drug release decreased as sintering time increased for all formulations, which is in accordance with previous studies (Rao *et al*., 2001; Rao *et al*., 2003). The retardation in drug release on sintering may be attributable to the wax particles soften during sintering and hence penetrated the empty spaces, forming a continuous sheet around the drug and other materials present in the formulation. This increased the surface area of wax which indicates a nearly monolithic formation. This decreased the exposure of the drug to the dissolution medium which resulted in the retardation of release of the drug from the matrix tablets. On the other hand, it may also be attributed to the increase in tablet hardness which resulted in a decrease in tablet porosity and hence a reduction in influx of the dissolution medium. The CB formulation had the same release pattern with all the formulations i.e. sintered and unsintered tablets. However, formulation CW6 has a comparable release profile with the CB formulation. The release parameters, m_∞, t_∞, m_∞/t_∞ for formulation CW6 and CB were 94.2%, 99.4%, 12h, 12h, 7.85**%**h^{-1}, 8.23**%**h^{-1} respectively. Formulation CW6 was taken as optimized formulation since it has comparable release profile with that of the CB formulation.

Drug release mechanism. The release data for all the tablets (i.e. sintered, unsintered and CB) were analyzed based on zero-order kinetics, first-order kinetics, Higuchi mechanism and Korsmeyer and peppas model to ascertain which release model fit best (Higuchi, 1963; Korsmeyer *et al*., 1983; Peppas, 1985; Harland *et al*., 1988). The values of the correlation coefficients (r) and the release rate constants are presented in table 3. The r-values for all the formulations were between 0.5920 and 0.8360 (zero order), 0.8820 to 0.9802 (first order), 0.8372 to 0.9531 (Higuchi) and 0.9601 to 0.9898 (Korsmeyer and Peppas). Hence, all the formulations fit best into Korsmeyer and Peppas model since they had r values ≥ 0.95. The value of release exponent (n) for all the formulations was < 0.5 (See Table 3). This indicates that release of diltiazem hydrochloride from these formulations followed Fickian diffusion mechanism (Korsmeyer *et al*., 1983).

FTIR. In order to investigate if there was any chemical interaction between added excipients and diltiazem hydrochloride in the optimized formulation (CW6) before and after sintering, the FTIR of the pure drug, carnuba wax, unsintered and sintered tablets were recorded (See Fig 3a,b,c and d respectively). The IR spectrum of diltiazem hydrochloride showed characteristic peaks at 1743.04 cm^{-1} (ester-C=O) and 1679.0 cm^{-1} (amide-C=O). However, for the carnauba wax alone (without drug or other excipients), IR spectrum showed signals at 2849.30 to 2918.46 cm^{-1} (C-H stretch), 1236.63 cm^{-1} (C=O stretch). Also, at a wavelength of 1736.63 cm^{-1} (C=O stretch) due to the presence of fatty esters in the carnauba wax.

Table 1: Effect of different sintering temperatures and times on physical parameters of the tablets.

Physical parameters	CW1	CW2	CW3	CW4	CW5	CW6	CW7	CB
Hardness (Kg/cm^2)	5.5±0.2	5.5±0.3	5.6±0.3	5.7±0.3	6.4±0.2	7.6±0.3	7.8±0.1	5.9±0.2
Friability (%)	0.52±0.01	0.53±0.02	0.50±0.03	0.50±0.01	0.32±0.03	0.30±0.02	0.28±0.03	0.34±0.03

Note: CW1 is unsintered tablet, CW2, CW3, CW4 are sintered tablets at 60^0C for 1, 3 and 5h respectively while CW5, CW6 and CW7 are sintered tablets at 70^0C for 1, 3 and 5h respectively. CB is commercial brand of diltiazem hydrochloride (Torrent Pharmaceutical Ltd) Manufacturing date: April 2009 and Expiring date March 2012.

Table 2: Dissolution parameters {m_∞ (%), t_∞(h), m_∞ / t_∞(%h^{-1})} of the different formulations

Formulations	CW1	CW2	CW3	CW4	CW5	CW6	CW7	CB
m_∞ (%)	97.4	96	94	96	98.3	91.2	83.5	99.4
t_∞(h)	4	4	6	8	10	12	12	12
m_∞ / t_∞ (%h^{-1})	24.4	24	15.7	12	9.8	7.6	6.96	8.23

Table 3: Correlation coefficient and release kinetics of diltiazem hydrochloride (n=3) from different formulations. Data analysed according to zero order, first order, Higuchi and Korsmeyer, and Peppas models.

Models	Zero		First		Higuchi		Korsmeyer and Peppas		
Formulations	r	k_0	r	k_1	R	k_H	r	n	k_2
CW1	0.592	19.3	0.9802	0.17	0.8835	49.4	0.9601	0.24	72.8
CW2	0.6129	19.1	0.9647	0.14	0.8965	48.2	0.9779	0.25	70.1
CW3	0.636	11.9	0.8478	0.06	0.8362	29.6	0.9399	0.23	59.7
CW4	0.6945	8.6	0.9602	0.06	0.9144	30.4	0.9898	0.28	52.6
CW5	0.6017	6.6	0.9289	0.05	0.8372	26.6	0.9722	0.22	60.3
CW6	0.7826	5.7	0.9214	0.03	0.9334	23.5	0.9779	0.27	45.8
CW7	0.7946	5.3	0.9011	0.02	0.9333	21.7	0.9703	0.28	41.1
CB	0.9069	6.0	0.8820	2.0	0.9733	13.7	0.9760	0.286	43.8

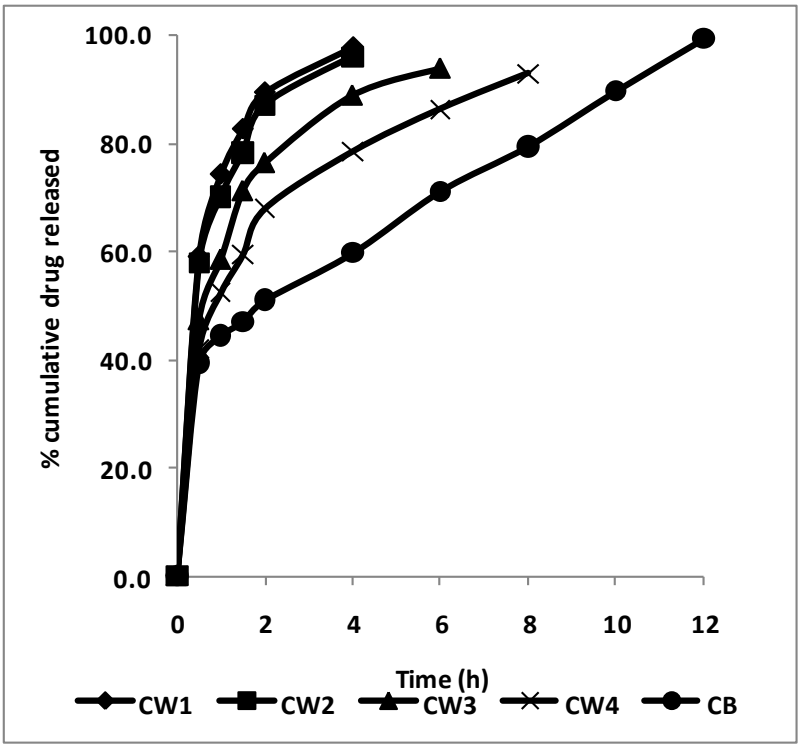

Fig 1: CW1 is unsintered tablets and CW2, CW3, CW4 are sintered tablets at 60^0C for 1, 3 and 5h respectively, while CB is the commercial formulation.

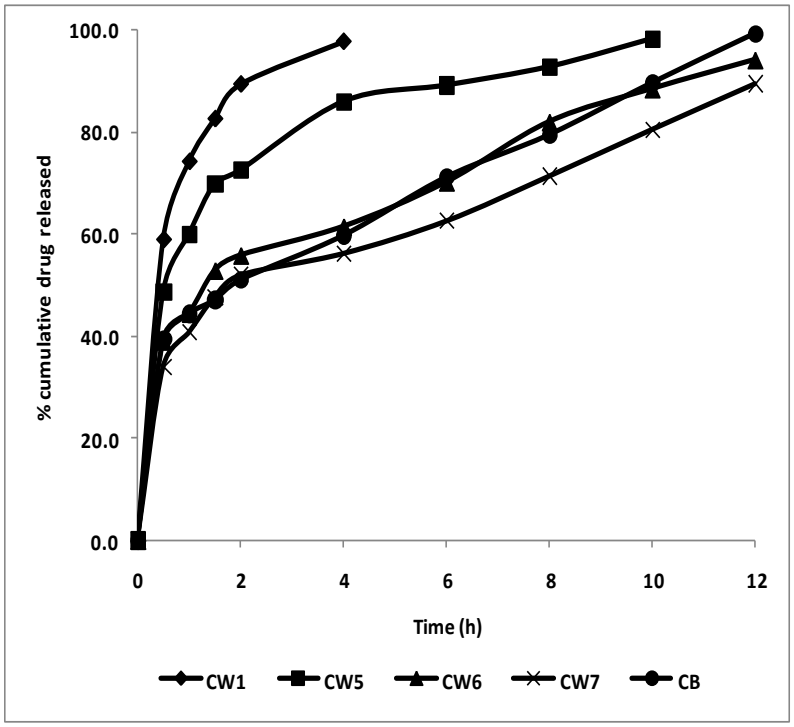

Fig 2: CW1 is unsintered tablets and CW5, CW6, CW7 are sintered tablets at 70^0C for 1, 3 and 5h respectively, while CB is the commercial formulation.

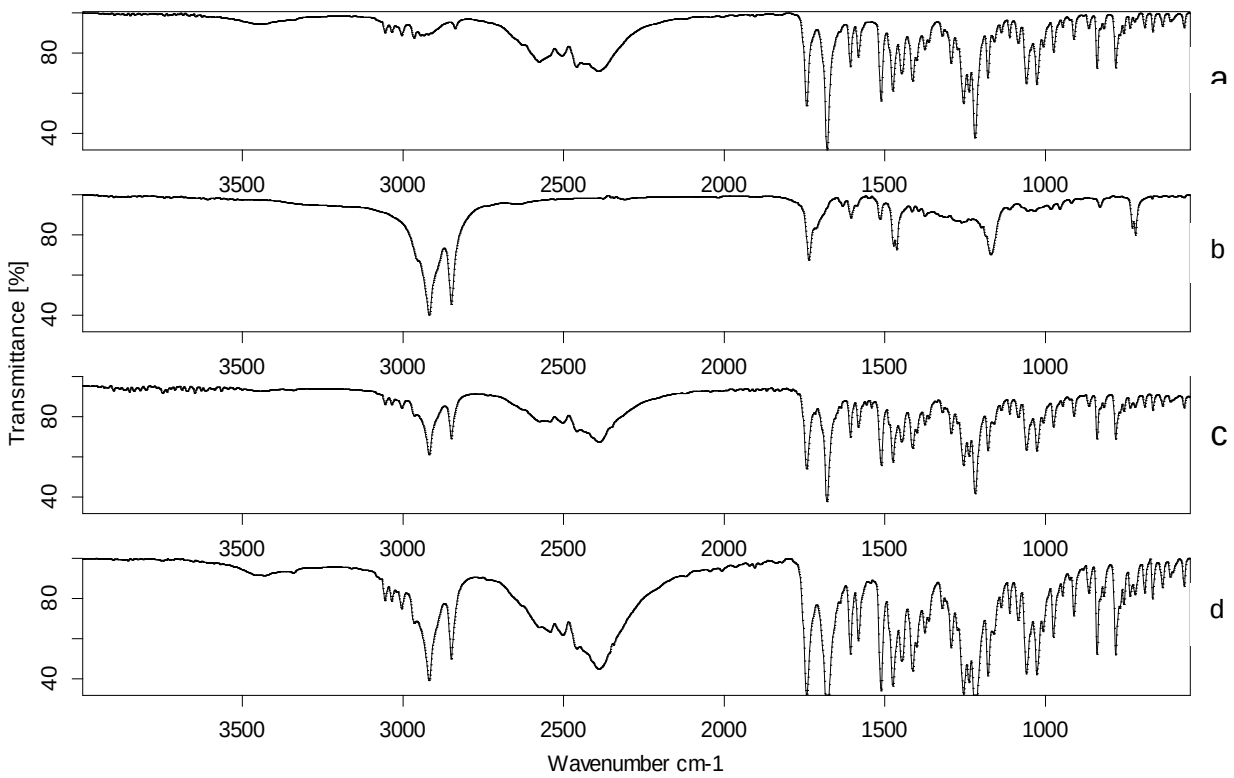

Fig 3: FTIR of (a) diltiazem hydrochloride, (b) carnuba wax, (c) unsintered diltiazem hydrochloride prepared with carnuba wax and (d) sintered diltiazem hydrochloride prepared with carnuba wax (d) and the complete spectra (e).

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These spectra were compared with the IR spectrum of the unsintered and the optimized sintered formulation (CW6). All the characteristic peaks observed for both drug and excipient remained unchanged and the spectra data was superimposed (See Fig 3). This observation ruled out the possibility of chemical interaction and complex formation between the diltiazem and added excipients (such as carnuba wax) before sintering and after sintering.

Conclusion: The conclusion is that sintering technique has been developed for the controlled release of diltiazem hydrochloride tablets. The extent of retardation depended on the sintering temperature and duration. The FTIR studies showed that diltiazem hydrochloride was not affected by the higher temperature used for sintering hence this type of technique which is easy and convenient can be used to achieve controlled release of oral solid dosage forms.

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