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Formulation of Verapamil Hydrochloride Matrix Granules by Sintering Technique and its Evaluation

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Abstract- Exploration of sintering concept in the pharmaceutical sciences is relatively recent. The aim of this study was to investigate the release characteristics of matrix granules consisting of hydrophobic (i.e waxy) material and Verapamil hydrochloride for sustained release application using thermal sintering technique. It was considered as an ideal drug for designing sustained release formulation on account of its high frequency of administration and short biological half life. Granules prepared by melt granulation technique were formulated with water soluble drug, carnauba wax, glyceryl behenate (a wax matrix forming polymer) lactose, magnesium stearate. Matrix granules of Verapamil hydrochloride prepared with various concentration of wax and polymer were sintered thermally at various times periods, temperature and were evaluated for physicochemical parameters and in vitro dissolution studies. The sintering time markedly affected the drug release properties of wax and polymer. It is notable that the release rate of Verapamil hydrochloride from granules was inversely related to the time of sintering. Sintering technique enhanced the extend of drug retardation from the systems studied.

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R. R. Bhagwat [α] & Dr. I. S. Vaidya [σ]

Abstract- Exploration of sintering concept in the pharmaceutical sciences is relatively recent. The aim of this study was to investigate the release characteristics of matrix granules consisting of hydrophobic (i.e waxy) material and Verapamil hydrochloride for sustained release application using thermal sintering technique. It was considered as an ideal drug for designing sustained release formulation on account of its high frequency of administration and short biological half life. Granules prepared by melt granulation technique were formulated with water soluble drug, carnauba wax, glyceryl behenate (a wax matrix forming polymer) lactose, magnesium stearate. Matrix granules of Verapamil hydrochloride prepared with various concentration of wax and polymer were sintered thermally at various times periods, temperature and were evaluated for physicochemical parameters and in vitro dissolution studies. The sintering time markedly affected the drug release properties of wax and polymer. It is notable that the release rate of Verapamil hydrochloride from granules was inversely related to the time of sintering. Sintering technique enhanced the extend of drug retardation from the systems studied.

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I. Introduction

Controlled drug delivery technology represents one of the most rapidly advancing areas of science. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity and improved patient compliance. [1]

Sintering is defined as the bonding as the bonding of adjacent particle surfaces in a mass of powder or in a compact by the application of heat. Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmosphere pressure. The sintering process has been used for the fabrication of sustained release matrix tablets and for the stabilisation of drug permeability of film coating derived from various pharmaceutical lattices.[2],[3],[4]

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Recently, Uhumwangho et al., (2011)[5] developed an oral sustained release dosage formulation of Diltiazem HCL wax matrix granules by sintering the polymer matrix using melt granulation technique. Flowerlet et al., (2010)[6] developed an oral sustained release dosage formulation of Metformin HCL matrix tablets by sintering the polymer matrix with organic vapour such as acetone. Polymer films with different permeability have been explored to modify drug release from drug particles. Some examples mentioned in the literature include films with the drug as a solution in a polymeric matrix. E.g. polymer coated reservoir devices (Lehmann et al. 1979)[7], polymeric colloidal particles (microparticles or nanoparticles) either in the form of reservoir or matrix devices (Oppenheim 191; Douglas et al 1987)[8]

These methods are however very complicated and expensive since it requires the use of organic solvents as coating fluid. However these organic solvents are hazardous to the environment. A simple approach which was considered in the present study, is melt granulation whereby the drug powder is triturated with a melted wax serving as a hydrophobic retard release agent. The resulting granules consist of the drug particles dispersed in a wax continuous matrix.

Verapamil Hydrochloride (VRH)[9],[10] is a vasodilator alkaloid found in the opium poppy. It is an L-type calcium channel blocker. It has been used in the treatment of hypertension, angina pectoris, cardiac arrhythmia. Its chemical formula is (RS) - 5 - [N - (3,4 - dimethoxy - phenethyl) methylamino] - 2 - (3,4 - dimethoxyphenyl) - 2 - isopropyl valeronitrile with a molecular weight 491.07. It has half life of about 4 to 6 hr. It is completely absorbed from GIT with usual dose of 40 to 240 mg 3 times a day.

The aim of this study was to prepare wax matrix granules by melt granulation technique using VRH as a model drug. These matrix granules were later subjected to thermal sintering at different time duration at different temperatures. Consequently, the effect of sintering temperature and duration on the drug release profiles and physicochemical parameters were investigated.

II. Materials and Methods

Materials: The active ingredient used in the study was verapamil hydrochloride (Piramal Healthcare, Hydrabad, India). The matrix material used was glyceryl behenate (Gattefose India Pvt Ltd.) carnauba wax (S D Fine Chemicals Mumbai). Other materials used were of analytical grade.

Melt granulation technique: Two waxes are studied here for the effect of thermal sintering on drug release. Both waxes (glyceryl behenate and carnauba wax) were melted individually in porcelain dish in a water bath at a temperature higher than its melting point i.e. 83ºC for glyceryl behenate and at 86ºC for carnauba wax. A sample of VRH powder was added to the melted wax and thoroughly mixed with a glass rod. It was then allowed to cool to room temperature (35ºC±2ºC). The mass was pressed through a sieve of mesh 12 to produce wax matrix granules.

Sintering of matrix granules: The matrix granules were then subjected to thermal treatment by placing them in aluminium foil and subjecting to sintering at different temperature i.e. 60ºC, 75ºC for different durations 1 and 3 hr for glyceryl behenate. For carnauba wax matrix granules it is 70ºC, 80ºC for durations 1 and 3 hr.

Packing property of the matrix granules[11]: The packing property was determined by measuring the difference between bulk density and tapped density using standard procedure. 20 g of matrix granules sample was placed in a 250 ml clean measuring cylinder and the volume V_o occupied by the sample without tapping was determined. An automated tap density tester was used for tapping the granules according to USP. After 100 taps the occupied volume V_{100} was noted. The bulk and tap densities were calculated from these volumes (V_o and V_{100}) using the formula Density = Weight/Volume occupied by sample. From the data Hauseners ratio was determined.

Flow property of matrix granules: The flowability of the granules was determined by measuring the angle of repose formed when a sample of the granules was allowed to fall freely from the stem of a funnel to a horizontal bench surface. The radius (r) and the height (h) of the powder heap were determined and then the angle of repose (θ) was calculated.

Encapsulation of the matrix granules: Samples of matrix granules before and after sintering were filled manually into plain hard gelatine capsules. The capsules were kept in airtight containers before their use in *in – vitro* dissolution studies.

In vitro dissolution test: One capsule filled with the matrix granules were placed in a cylindrical basket (aperture size 425μm; diameter 20mm; height 25mm), and immersed in 1000ml of water with pH 3. The fluid was stirred at 75 rpm. Samples of the medium (5ml) were withdrawn at selected time intervals and replaced with an equal volume of drug free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analysed for content of Verapamil HCL at λmax 278nm by using a double beam spectrophotometer. The samples were filtered with Whatman No 3 filter paper before assay and the amounts released were 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. Individual results were reproducible to ±10% of the mean.

Fourier Transform Infra red (FTIR) : The FTIR spectrum of the different samples were recorded in an Infra Red spectrometer using potassium bromide discs prepared from powdered samples. Infrared spectrum was recorded in the region 4000 to 400 cm^{-1}.

Determination of rate order kinetics and mechanism: The dissolution data were analysed on the basis of zero order (cumulative amount of drug release 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[12] and Peppas[13] (log cumulative amount released vs log time). These are the most frequently reported kinetics of drug release from drug particles and their solid dosage forms.

III. Results and Discussion

Effects of sintering on physicochemical parameters of unsintered and sintered wax matrix granules: The effects of sintering on the physic-chemical parameters of unsintered and sintered matrix granules are presented in table 1 & 2. It was observed that all the matrix granules were free flowing with angle of repose ≤ 29ºC. No much difference was observed between the unsintered and sintered batches at different temperatures for different durations.

Table 1

Parameters Evaluated	Unsintered	Sintered at 60º C		Sintered at 75º C		Sintered at 60º C		Sintered at 75º C		
	UF 1	S1	S2	S3	S4	S5	S6	S7		S8
Bulk density	0.55	0.56	0.55	0.55	0.53	0.54	0.53	0.52		0.51
Tap density	0.65	0.67	0.66	0.64	0.65	0.63	0.61	0.64		0.60
Carr's index	20.73	15.38	9.72	10.1	17.33	14.28	13.11	18.75		15.00
Angle of repose	28.47	27.1	27.0	25.4	25.4	28.1	28.7	29		28.9
Hausners ratio	1.18	1.19	1.2	1.16	1.22	1.16		1.15	1.23	1.17

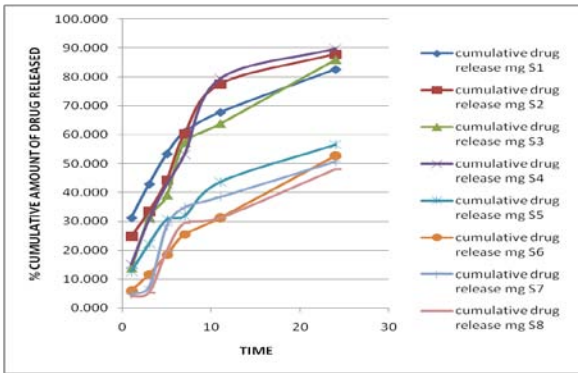
Table 2

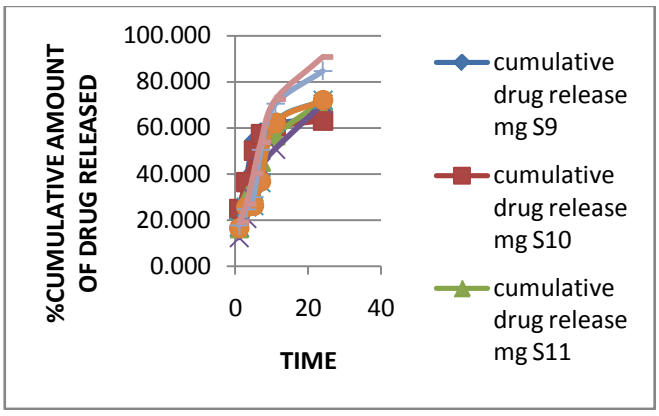
Parameters Evaluated	Unsintered	Sintered at 70º C		Sintered at 80º C		Sintered at 70º C		Sintered at 80º C	
	UF 2	S9	S10	S11	S12	S13	S14	S15	S16
Bulk density	0.55	0.56	0.55	0.55	0.53	0.50	0.51	0.53	0.50
Tap density	0.65	0.67	0.66	0.64	0.65	0.60	0.64	0.63	0.63
Carr's index	19.27	19.8	15.27	14.47	10.81	16.66	20.31	15.87	20.63
Angle of repose	28.47	27.1	27.0	25.4	25.4	26.2	26.3	29.6	29.7
Hausners ratio	1.18	1.19	1.2	1.16	1.22	1.2	1.25	1.18	1.26

Composition of different formulations (mg/capsule) :

Formulation code	F1 (S1 – S4)	F2 (S5 - S8)	F3 (S9 – S12)	F4 (S13 – S16)
Ingredients				
Drug	120	120	120	120
Glyceryl behenate	60	120	–	–
Carnauba wax	–	–	60	120
Lactose	97	37	97	37
Magnesium stearate	2.8	2.8	2.8	2.8

Dissolution profiles of matrix granules: The dissolution profiles of the unsintered and sintered matrix granules at 60, 75, 70, 80ºC at different time durations are presented in fig. It was observed that the unsintered matrix granules were able to retard the drug for 7hr. Generally, as the temperature and duration of sintering of the matrix granules increased the time to attain maximum release increased correspondingly.





Drug release mechanism: A good knowledge of the drug release kinetics will provide a proper understanding of the drug release mechanism. Four mathematical models were used for analysis: zero order kinetics, first order kinetics Higuchi mechanism and Korsmeyer and Pepps model.

FTIR: Formulation S4 and S16 were considered for FTIR studies since it was able to retard the drug for a period 24 hr. This study was carried out in order to investigate if there was any chemical interaction between added excipients and VRH in the formulation S4 and S16.before and after sintering. The FTIR of the pure drug, glyceryl behenate, carnauba wax, sintered matrix granules were recorded. The IR spectrum of VRH showed characteristic peaks at 2240cm^{-1} (for C=N of saturated alkyl nitrile) 2542cm^{-1} (broad complex band due to N-H stretch in amine group). It was observed that the IR spectra showed both the principal peaks of VRH in sintered matrix granules also. It suggests that there was no chemical interaction between the VRH and added excipients.

Conclusion: The use of lipophilic substances as release retarding agents is widely accepted concept because of their effectiveness in drug release control and low cost of manufacturing. The use of sintering technique adds to the effectiveness of polymers to extend the release of drug from formulation depending upon the duration and temperature of sintering. Sintering technique enhanced the extent of drug retardation from the systems studied. Formulation S16 sintered at 80ºC for 3hr with carnauba wax and 75ºC for 3hr with glyceryl behenate was able to sustain the drug for a period of 24hr with a maximum release of 84% and 89%. The FTIR studies showed that the model drug was not affected by the temperature and time duration used for sintering.

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