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Original Article

Thermal Sintering Technique: A Novel Strategy Used in the Design of Gastro Retentive Floating Matrix Tablets of Nicardipine HCl and Its Evaluation

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ABSTRACT

Exploration of sintering technique in the pharmaceutical sciences is relatively recent. The aim of the present study was to prepare thermally sintered floating matrix tablets of Nicardipine HCL (NIC) and to study the effect of sintering conditions on *in-vitro* dissolution study, *in-vitro* buoyancy properties, hardness and friability. The tablets were prepared by direct compression method using HPMC K100M as matrix forming polymer and sodium bicarbonate as gas generating agent. The prepared tablets were sintered at two different temperatures like 60^{0}C and 70^{0}C for two different time periods 1.5 hr and 3 hr in a hot air oven. The results showed that the release rate of the drug was inversely related to the sintering temperature and the time of sintering. Increasing the temperature or time of exposure to a particular temperature often decreased the release rate of the drug. By using sintering technique floating lag time and total floating time of tablets was found to be decreased and increased respectively, with increase in the sintering temperature and sintering time. In addition the hardness of the sintered tablets was increased with increase in sintering temperature and duration of sintering, where as friability of tablets was found to be decreased with increasing sintering time. An optimised formulation F2 sintered at 70^{0}c for 3 hr was selected based on their drug retarding properties and comparatively low proportion of polymer. The optimised formulation followed Korsmeyer-Peppas release kinetics with Fickian diffusion mechanism. There was no evidence of interaction between the drug and polymer used as shown in the FTIR studies.

Key words: Sintering, Gastro retentive floating tablet (GRFT), Nicardipine HCL (NIC), Matrix Tablet.

1. INTRODUCTION

The concept of the sintering technique in the pharmaceutical sciences is relatively new, but research interests regarding this technique have been continuously growing.The thermal sintering technique

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involves the exposure of the polymer matrix to its glass transition temperature, in which there is slow softening and fusion of polymer particles & formation of welded bond between them. The drug particles are entrapped in the formed matrix which results in the controlled release of drug[1]. In the pharmaceutical science, sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powders at elevated temperatures, for solid-bond formation during tablet compression, and for thermal curing of polymer-latex film coatings. The sintering process has been used for the fabrication of sustained – release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices.[2, 3]

The systemic bioavailability of Nicardipine HCL (NIC) is only 20 -33% (undergoes extensive first-pass metabolism) and the drug need to be administered frequently (30 mg, thrice daily) due to its short half life (2-4 hr). Moreover NIC is absorbed only in stomach and upper part of GIT because of its good solubility at low P^H [4]. Since there are very few reports on gastro retentive floating drug delivery system with sintering technique, the objective of the present work was to develop sustained release floating matrix tablet of NIC by sintering technique to extend the gastric residence time and to prolong the drug release.

2. MATERIALS AND METHODS

Materials

Nicardipine HCL (NIC) was obtained as Gift sample from DR. Reddy's Laboratories ltd, Hyderabad. Sodium bicarbonate and Magnesium sterate were procured from Lobachem Pvt Ltd Mumbai. HPMC K100M was provided by Aurobindo Pharma Ltd, Hyderabad. All chemicals other reagents and used for the study were of analytical grade.

Preparation of gastro retentive floating tablets (GRFT) of Nicardipine HCL

The tablets are prepared by direct compression method with different composition as shown in Table 1**.** The measured quantity of drug, polymers and excipients were mixed homogeneously in a glass mortar for 15 min. The mixture was then compressed into tablets using an 8 mm, biconcave punch, 16-station rotary tablet machine **(**Cadmach, Ahmedabad, India).

Preparation of thermally sintered gastro retentive floating tablets (TSGRFT) of Nicardipine HCL

The prepared tablets were exposed at two different constant temperatures like 60^0C and 70^0C for two different periods like 1.5 hr and 3 hr in a hot air oven. The temperature of the oven was maintained constantly. After exposing to the respective temperature and time tablets are removed, cooled to room temperature and stored in closed desiccators for further use.

Table 1: Composition of gastro retentive floating tablets (GRFT) of Nicardipine HCL

Ingredients*	F 1	F 2	F 3
Nicardipine HCL	40	40	40
HPMC K100M	80	90	100
Sodium Biocarbonate	20	22	24
Magnesium Stearate	2	2	2
Total weight (mg)	**142**	**154**	**166**

*All the ingredients are in milligram per tablet

Evaluation of Unsintered and Sintered floating tablets of Nicardipine HCL

The Unsintered and Sintered floating tablets of Nicardipine HCL are evaluated for various physiochemical parameters like hardness, friability, drug content uniformity, floating lag time, total floating time and *in vitro* dissolution studies.

Buoyancy test [5-8]

The buoyancy of tablets was studied by placing them in a 1L glass beaker containing 900 ml of 0.1N HCl. The time required for the tablet to emerge to the surface and float was determined as floating lag time and duration of time for which dosage form remain

buoyant was determined as Total Floating Time. All the formulated floating tablets are subjected to *In vitro* buoyancy studies in triplicate for each batch of tablets.

***In vitro* dissolution studies[9]**

The *In vitro* dissolution study was performed by using the United States Pharmacopoeia (USP) XXIV basket apparatus. The dissolution medium consisted of 900 ml of 0.1 N HCL. The test was conducted at $37^0C \pm 0.5^0C$ and at 50 rpm. Five ml samples were withdrawn at predetermined time intervals and the same volume was replaced immediately with fresh medium. After the filtered samples were suitably diluted with dissolution medium the absorbance of the samples was measured at 239 nm using double beam UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate.

Release Kinetics [1, 3]

Data obtained from the *in-vitro* dissolution studies was fit into various equations and kinetic models to explain the release kinetics of Nicardipine HCL from floating tablets**.** The dissolution data were analyzed on the basis of zero order rate (cumulative percentage amount of drug released vs. time), first order rate (log cumulative percentage amount of drug remaining vs. time), Higuchi model (cumulative percentage amount of drug released vs. square root of time), Hixon-Crowell (cube root of drug percentage remaining in matrix vs. time) and Korsmeyer and Peppas model (log cumulative percentage amount released vs. log time)**.**The model with highest correlation coefficient (R) was considered to be the more appropriate model for the dissolution data. The kinetic models used were zero-order equation (eq. 1), first-order equation (eq. 2), Higuhi equation (eq. 3), krosmeyer-peppas equation (eq. 4), and Hixon-Crowell equation (eq. 5).

$Qt = Q_0 + K_0t$ ---------- (1)

$\log C = \log C_0 – K_1t/2.303$ ---------- (2)

$Q_t = K_H.t^{1/2}$ ---------- (3)

$(W_0^{1/3} - W_t^{1/3}) = K_{HC}\, t$ ---------- (4)

$Mt/M_\infty = K_K.t^{n}$ ---------- (5)

Qt: amount of drug released in time t, Q_0: initial amount of drug in the tablet, C_0:Initial concentration of drug, Q: active fraction released per unit of surface, W_0: initial amount of drug in the pharmaceutical dosage form, Wt: remaining amount of drug in the pharmaceutical dosage form at time t, Mt: The amount of drug released at time t and M_∞: Amount released at time ∞, thus the Mt\M∞: Fraction of drug released at time t. K_0, K_1, K_H, K_{HC}, and K_k are release rate constants for Zero-order, First-order, Higuchi, Hixon-Crowell, and Koresmeyer-Peppas model respectively.

According to the Korsmeyer-Peppas equation, the release exponent ‘n’ value is used to characterize different release mechanisms. If the n value is 0.45, the release mechanism follows Fickian diffusion. If n value is $0.45 < n < 0.89$ (for cylindrical), the mechanism follows a non-Fickian (anomalous) diffusion and when n=0.89 it will be a non Fickian case II transport and if n>0.89 it will be a non-Fickian super case II transport.

Drug-polymer-excipient compatibility studies

The compatibility between Drug-polymer-excipient can be confirmed by Fourier transforms infrared spectroscopy (FTIR). A FTIR (Thermo-Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - $400cm^{-1}$. A quality equivalent to 2mg of pure drug was used for the study.

3. RESULTS AND DISCUSSION

All the unsintered (initial tablets) and thermally sintered tablets passed the physicochemical tests concerning hardness, friability, drug content uniformity. The results are shown in table no. 2.

For all the formulations Floating lag times were in the range of 96 to 223 sec. Floating lag time was found to be decreased with increase in the sintering temperature, which might be due to decreasing porosity. When the tablets were exposed to sintering temperature, the void

spaces between the particles of the tablets may be decreased and each particle was exposed to the gastric fluid quickly.

Total floating time of all the formulations was found to be in the range of 11-14 hrs (table 2).It was also observed that as the sintering temperature was increased total floating time was increased. This is might be attributed to the formation of welded bonds between the particles by softening and fusion of polymer particles, which makes tablet intact for longer period.

The hardness for all the formulations was found to be in the range of 3.3 kg/cm ^{2} to 5.8 kg/cm ^{2}. The hardness of the sintered tablets were found to be increased with increase in sintering temperature and duration of sintering, may be due to the formation of welded bond among the polymer after sintering condition.

For both the sintered and unsintered tablets the percentage weight loss in the friability test was found to be less than 0.8% in all formulations, which ensures that tablets are mechanically stable. Friability of tablets was found to be decreased with increasing sintering time. Hence by using thermal sintering technique friability of tablets can be reduced.

Table 2: Physico-chemical properties and Buoyancy characteristics of prepared unsintered and sintered GFRT of Nicardipine HCl

Sintering temperature and time	Hardness# (Kg/cm^2)	Friability* (%)	Drug content## (%)	Floating lag time** (Sec)	Total floating time** (hr)
FORMULATION F1					
Unsintered	3.3	0.68	99.16±0.51	223±2	11±0.8
60^0-1.5 hr	3.7	0.60	98.44±0.84	207±3	13±0.5
60^0-3 hr	4.2	0.56	97.68±1.08	192±8	15±1.0
70^0-1.5 hr	4.4	0.48	99.92±0.32	185±9	16±1.0
70^0-3 hr	4.7	0.44	99.53±0.94	175±2	17±0.5
FORMULATION F2					
Unsintered	3.5	0.67	98.97±1.09	176±4	10±1.0
60^0-1.5 hr	4.2	0.58	99.68±0.67	166±5	12±1.0
60^0-3 hr	4.4	0.53	98.56±1.12	154±2	13±1.0
70^0-1.5 hr	5.5	0.45	99.18±0.86	150±4	14±0.5
70^0-3 hr	5.6	0.40	98.54±0.45	144±7	15±0.5
FORMULATION F3					
Unsintered	4.0	0.63	97.68±0.74	139±2	09±1.0
60^0-1.5 hr	4.4	0.46	97.87±0.39	127±8	11±1.0
60^0-3 hr	5.0	0.41	99.78±0.12	111±3	13±1.0
70^0-1.5 hr	5.2	0.37	98.45±0.87	107±4	13±1.0
70^0-3 hr	5.8	0.31	100.88±1.27	96±8	14±1.0

#: n=5; *: n=10; ##:Mean±S.D (n=3); **: Mean±S.D (n=5).

The sintering temperature and time markedly affected the drug (NIC) release properties from the sintered GRFT. From the *In vitro* dissolution profile (cumulative percentage drug released) as shown in Fig. 1-3.

The formulation of F1 without sintering condition released more than 95% of the drug in 7 hrs only and tablets of same formulation sintered at 60^{0}C for 1.5 hr and 3 hr retarded the drug release up to 9 hrs and 10 hrs respectively, while at 70^{0}C for 1.5 hr and 3 hr retarded the drug release up to 9 hrs and 10 hrs respectively.

The formulation of F2 without sintering condition released more than 95% of the drug in 8 hrs only and tablets of same formulation sintered at 60^{0}C for 1.5 hr and 3 hr retarded the drug release up to 10 hrs and 11 hrs respectively, while at 70^{0}C for 1.5 hr and 3 hr retarded the drug release up to12 hrs and 13 hrs respectively.

The formulation of F3 without sintering condition released more than 95% of the drug in 9 hrs only and tablets of same formulation sintered at 60^{0}C for 1.5 hr and 3 hr retarded the drug release up to 11 hrs and 12 hrs respectively, while at 70^{0}C for 1.5 hr and 3 hr retarded the drug release up to 12 hrs and 14 hrs respectively.

It was found that the release rate of the drug was inversely related to the sintering temperature and the sintering time. Increasing the temperature or time of exposure to a particular temperature often decreased the release rate. This is due to the slow softening and fusion of polymer particles & formation of welded bond between them. The drug particles are entrapped in the formed matrix which results in the controlled release of drug. It was also observed that the release rate of the drug was decreased as the concentrations of polymer increased, which may be due to increased

intensity of air pockets surrounding the jellified tablet surface.

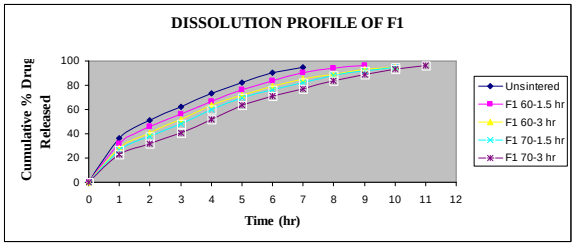

Fig 1: **Dissolution profiles of unsintered and thermally sintered floating tablets of formulation F1**

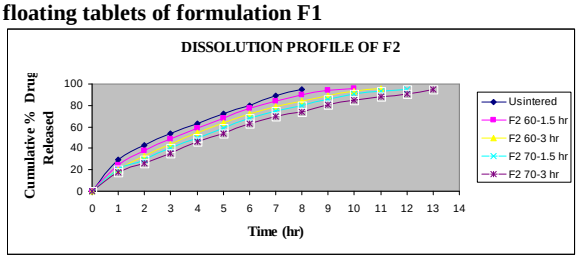

Fig 2: **Dissolution profiles of unsintered and thermally sintered floating tablets of formulation F2**

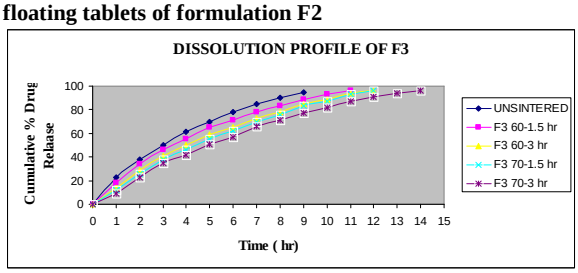

Fig 3: **Dissolution profiles of unsintered and thermally sintered floating tablets of formulation F3**

Based on the drug release retarding properties and comparatively low proportion of polymer formulation F2 sintered at 70^0c for 3 hr was selected as optimised formulation.

The results of dissolution data fitted to various kinetic models including regression coefficients are given in table no.3. The coefficients of regression for all the formulations were in the range between 0.7209-0.8673 (Zero-order), 0.8923-0.9779 (First-order), 0.9198-0.9860 (Higuchi), 0.9757-0.9995 (Koresmeyer-Peppas), and 0.8475-0.9068 (Hixon-Crowell). Korsmeyer-Peppas model was found to be the best fitted for optimised formulation dissolution profile. The 'n' values were found to be < 0.45 for the optimised formulation (formulation F2 sintered at 70^0c for 3 hr). This indicates that drug release occurred from the optimised formulation followed Fickian diffusion mechanism.

Table 3: Drug Release Kinetic Studies of unsintered and sintered floating tablets of Nicardipine HCl

Formulations	Zero Order (r)	First Order (r)	Higuchi (r)	Hixon Crowell (r)	Koresmeyer Peppas (r)	(n)
F1 Unsintered	0.7209	0.9154	0.9198	0.8596	0.9995	0.2580
F1 60^0-1.5 hr	0.7432	0.9060	0.9322	0.8580	0.9995	0.2709
F1 60^0-3 hr	0.7706	0.9137	0.9523	0.8733	0.9987	0.3000
F1 70^0-1.5 hr	0.8003	0.9259	0.9602	0.8902	0.9929	0.2995
F1 70^0-3 hr	0.8391	0.9352	0.9723	0.9086	0.9823	0.3175
F2 Unsintered	0.7466	0.8923	0.9365	0.8485	0.9980	0.2847
F2 60^0-1.5 hr	0.7906	0.9104	0.9611	0.8748	0.9985	0.3270
F2 60^0-3 hr	0.8312	0.9283	0.9793	0.8998	0.9991	0.3669
F2 70^0-1.5 hr	0.8370	0.9779	0.9779	0.8981	0.9908	0.3440
F2 70^0-3 hr	0.8530	0.9269	0.9828	0.9049	0.9888	0.3500
F3 Unsintered	0.8062	0.9246	0.9694	0.8900	0.9979	0.3510
F3 60^0-1.5 hr	0.8253	0.9228	0.9769	0.8939	0.9907	0.4006
F3 60^0-3 hr	0.8477	0.9254	0.9845	0.9020	0.9880	0.4514
F3 70^0-1.5 hr	0.8573	0.9246	0.9860	0.9041	0.9857	0.4775
F3 70^0-3 hr	0.8673	0.9243	0.9848	0.9068	0.9757	0.5423

From the FTIR study it was observed that the spectrum peak points of the optimised formulation were similar with that of the pure NIC, which clearly indicating that there is no drug-polymer interaction.

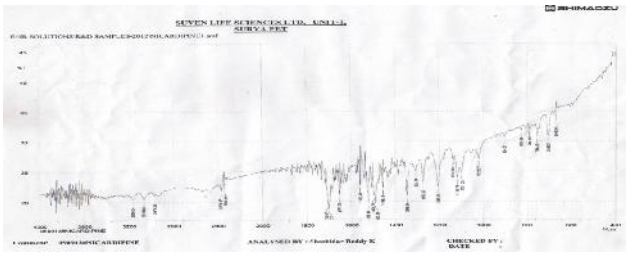

Fig 4: FTIR spectrum Pure Nicardipine hydrochloride

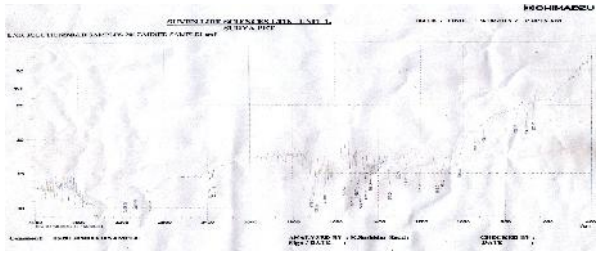

Fig 5: FTIR spectrum optimised formulation

4. CONCLUSION

From the above study and its evaluation parameters it can be concluded that a simple technique of thermal sintering may be used in the design of GRFT of Nicardipine HCL to sustain the drug release, decrease the floating lag time, increase total floating time,

prolong the gastric residence time and ultimately its bioavailability.

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