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Research Article

Incorporation of Certain Hydrophobic Excipients in the Core of Melt Granules of Paracetamol and the Effect on Drug Release Profiles

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Abstract

Objective - *A process of melt granulation whereby the drug powder is mixed with a melted wax has been used to modify the dissolution rates of drug particles. The present study investigated how the incorporation of hydrophobic materials (talc or magnesium stearate) in the core of such granules may further retard drug release.*

Method - *The hydrophobic powder was mixed with the drug (paracetamol) powder prior to melt granulation with Carnuba wax. Content of the hydrophobic material varied from 0 to 50% but the content of wax was constant. Conventional granules of paracetamol were formed by wet massing the paracetamol powder with starch mucilage 20%w/v, followed by screening and drying. The granules were subjected to dissolution test.*

Results - *The results indicated that melt granulation remarkably retarded the dissolution rates of paracetamol granules. The rates can be further retarded by inclusion of an internal hydrophobic material. The dissolution rate of the conventional granules was 32%h^{-1} as against 11.6%h^{-1} (melt granules) and 10.3%h^{-1} (melt granules with intragranular hydrophobic agents, 5%w/w).*

Conclusion - *The indication is that the inclusion of an intragranular hydrophobic agent in the melt granules can be used to obtain further control of drug release*

Keywords: *carnuba wax, controlled release, talc, and magnesium stearate*

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INTRODUCTION

Controlled release solid dosage forms are available either as single unit or as multiple unit forms[1, 2]. A multiunit dosage form thus consists of particles (units) of differing release profiles with respect to onset, rate and the maximum release, etc. Controlled-release products are designed to decrease the dosing frequency and enhance patient compliance. In the last two decades, sustained - release dosage forms have made significant progress in terms of clinical efficacy and patient compliance[3].

Preparation of drug - embedded matrix tablets that involves the direct compression of a blend of drug and the matrix forming additives is one of the least complicated approaches for delivering drug in a controlled release pattern into the systemic circulation[4]. In an alternative approach, a combination of talc and magnesium stearate has been used to achieve zero -order release of ibuprofen from extended release tablets[5]. Talc is mainly used as a glidant and magnesium stearate as a lubricant in tablet formulations. Both materials are hydrophobic with a potential to repel water influx into tablets, hence retard drug release from such tablets. Previous studies[6, 7] have also shown that melt granulation (whereby the drug powder is triturated with a melted wax to form granules) is an effective means of retarding drug from drug particles. More recently, this technique has been used to retard the release of paracetamol from its melt granules using goat wax, carnuba wax and glyceryl monosterate in the melt granulation[8].

The purpose of the present study is to investigate how incorporation of hydrophobic agents (talc and magnesium stearate) will further modify the release profiles of the melt granules. The study thus sought for a simple approach for effectively modifying drug release from granules. Such granules could ultimately be encapsulated or tableted for multi-unit dose applications.

MATERIALS AND METHODS

Materials

Carnuba wax (Halewood Chemicals Ltd, England) was used in the melt granulation. It is a fine waxy solid with melting point of 82-88^{0}C, yellowish in colour. It was selected as material for coating because it is not sticky; hence it produces free flowing granules compared with other wax materials (i.e., goat fat and glyceryl monosterate). Talc (Get-Rid Pharm Pvt, Ltd, Pune, India) and magnesium stearate (BDH, Poole, UK). The test drug, paracetamol, was supplied by BDH (Poole, UK). Although sustained release formulations are usually applied to potent drugs with short biologic half - life, a readily available drug (paracetamol) was used to demonstrate the principle of retard release by melt granulation.

Methods

Melt granulation technique

Carnuba wax (20g) was melted in a stainless steel container in a water bath at a temperature higher than the melting point of the wax material (i.e., 90^{0}C). Paracetamol and the hydrophobic material (i.e., talc or magnesium stearate powder) were blended in varying proportions (Table 1). A sample of the paracetamol alone or the powder mixture (80g) was mixed with the melted wax in a Kenwood mixer (Model A901P England). The mass was pressed through a sieve of 710μm aperture size and dried in a vacuum oven (model A2904, Gallenkamp, England) at 25^{0}C for 1h. Convectional granules of paracetamol were produced by wet massing a sample of the paracetamol powder (100g) with 20%w/v starch mucilage (38ml). The wet mass was screened and dried in a vacuum oven at 25^{0}C for 1h. Moisture content of the resulting granules were 2.3±1.1%w/w (conventional granulation) and 2.1±1.5%w/w (melt granulation).

Dissolution test

Fines of size (< 210μm) were removed from the granules by sieving. A sample of the granules (500mg) was filled into a capsule shell and placed in a cylindrical basket (aperture size 425μm, diameter 20mm; height 30mm), which was immersed in 800ml of leaching fluid (0.1N hydrochloric acid maintained at 37 ± 2^{o}C). The fluid was stirred at 100rpm with a single blade GallenKamp stirrer (Model APP No 4B 5784A. Cat No: SS530). Samples (5ml) were withdrawn from the leaching fluid at selected time intervals with a pipette fitted with a cotton wool plug,

Table 1: Composition of the melt granules with varying content of hydrophobic agent (talc or magnesium stearate) in the core

Hydrophobic agent (g)	Paracetamol powder (g)	% hydrophobic agent in the powder mixture
0	80	0
4	76	5
8	72	10
16	64	20
24	56	30
32	48	40
40	40	50

Note: *This powder mixture was in turn mixed with the melted wax in the ratio 80:20 (powder: wax).*

Table 2: Release parameters showing the effect of incorporating the hydrophobic agent in the core of the melted granules

Release parameters Hydrophobic content, %	m_∞ (%)		t_∞ (h)		Release rate $\%h^{-1}$	
	Talc	Magnesium stearate	Talc	Magnesium stearate	Talc	Magnesium Stearate
0	93	93	8	8	11.6	11.6
5	93	92	9	9	10.3	10.2
10	92	92	9	9	10.2	10.2
20	92	92	9	9	10.2	10.2
30	92	91	9	10	10.2	9.1
40	91	90	10	10	9.1	9
50	90	90	10	10	9	9

Note: *0% means no hydrophobic agent was added.*

replacing with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and analysed for content of paracetamol spectrophotometrically at λ_{max}, 245nm using Spectronic 21D, (Bausch and Lomb, USA). For the wax-coated granules, the samples were kept in the fridge overnight to allow solidification of the melted wax, which may have leached during the dissolution test. The samples were filtered before assay. The amounts released were expressed as a percentage of the initial amount of drug in the granule samples. The determination was carried out in triplicate and the mean results reported. Plots of amounts released (%) vs time were constructed. The release rates were obtained from the slopes of the linear portions of the plots. Other parameters obtained from the plots were the maximum release (m_∞) and the time to attain it (t_∞).

RESULTS

Effect of melt granulation on the release profiles of the drug particles

The effect of melt granulation on the release profiles of paracetamol is shown in Fig 1. The melt granulations displayed a retarded release compared with the conventional granules. For instance, with the convectional granules, maximal release was achieved in 3h and the dissolution rate was $32.3\%h^{-1}$. After melt granulation with the carnuba wax, maximal release was now achieved in 8h, with a dissolution rate of $11.6\%h^{-1}$.

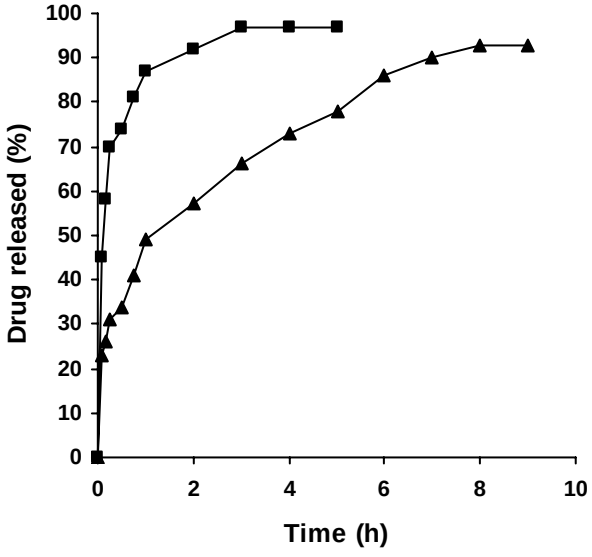

Fig 1: Release profiles from conventional (■) and melted (▲) granules of paracetamol.

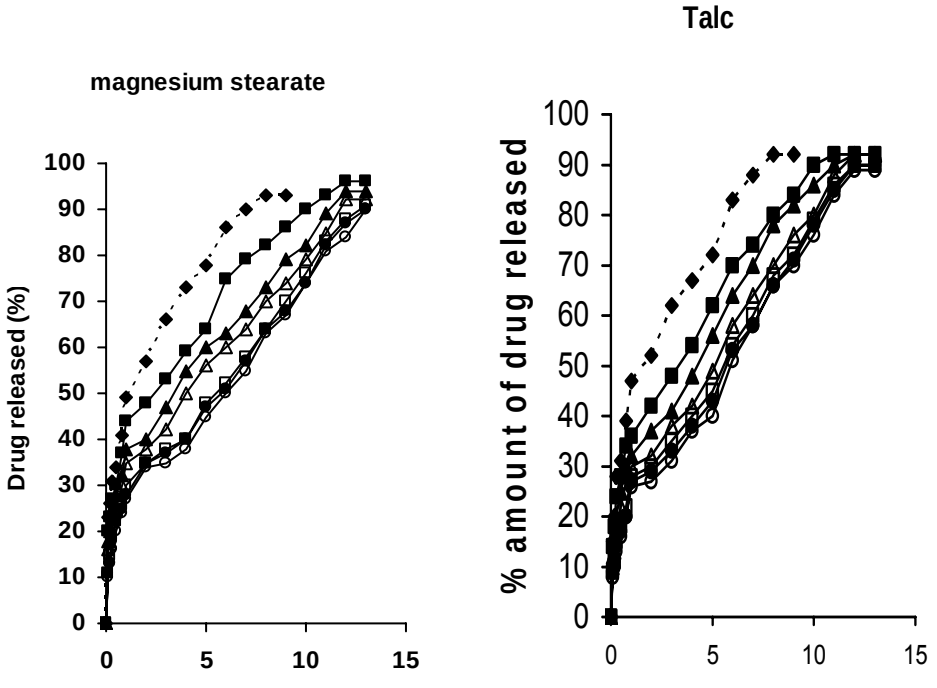

Fig 2: Effect of incorporation of a hydrophobic agent (HA) on drug release profile of the melt granules. Content of HA 0%w/w (…♦…), 5%w/w (■), 10%w/w (▲), 20%w/w (△), 30%w/w (□), 40%w/w (•), and 50%w/w (○).

Effect of incorporation of hydrophobic agents on the drug release profiles of the melt granules.

The results on the effect of incorporation of hydrophobic agents (i.e., talc or magnesium stearate) on the drug release profiles of the melt granulations are presented in Fig 2. The results showed that the release rates of the melt granulations were further retarded following the incorporation of a hydrophobic agent (i.e., talc or magnesium stearate) particularly when the talc or magnesium stearate content of the granules was ≥ 30%w/w. For instance, with the melted granules only (no hydrophobic agent), maximal drug release was achieved in 8h. When hydrophobic agents were incorporated in the granules (30%w/w), maximal release was now achieved in 10h. In other words, maximum release was prolonged by a further 2h. However, increase in the hydrophobic agent content beyond 30%w/w did not retard the extent of drug release further (Table 2). Hence, 30%w/w was considered as the optimal concentration of the hydrophobic agent to be used in the formulation of the retard release granules. The release data in Table 2 also showed that talc and magnesium stearate were equivalent in retarding drug release from the granules.

DISCUSSION

Regression analysis of the dissolution data on the basis of zero order, first order and Higuchi square root of time kinetics revealed that drug release from the melt granulations was generally consistent with the Higuchi kinetics ($R^2 \geq 98$). On the other hand, R^2 values for the conventional granules were generally low but increased to ≥ 95 when the data were plotted on the basis of an initial zero order (first 55% release) followed by a first order profile for the remaining 45%. The zero/ first order profile for the conventional granules indicates a dissolution (erosion) mechanism[8], while the Higuchi kinetic for the melt granulations indicates a diffusion controlled mechanism[9]. Therefore, the melt granules are more adaptable for prolonged release applications. The further retardation of drug release by the hydrophobic agents is attributable to the water repellant property of such agents.

CONCLUSION

The study showed that drug release from melt granulations could be effectively modified by intragranular incorporation of hydrophobic excipients (talc or magnesium stearate) to achieve retard drug release. The approach thus provides a means of further controlling drug release from the melt granulations. This finding can be exploited in the design of multi-unit dosage forms which provide a prompt release (from conventional granules) followed by a sustained release (from the melt granulations), which is desirable for drugs with short biologic half life.

REFERENCES

1. *Follonier N, Doelker E. Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms. STP Pharma Sci. 1992; 2:141-155.*
2. *Vial-Bernasconi AC, Doelker E, Buri P. Prolonged release capsules: divided and monolithic forms. STP Pharma Sci. 1988; 4: 397-409.*
3. *Merkus FWHM. Controlled and rate-controlled drug elivery; principal characteristics, possibilities and limitations, In: Struyker-Boudier, HAJ. (eds), Rate-Controlled Drug Administration and Action, CRC Press, Boca Raton, FL, USA, 1986 pp 15-47.*
4. *Cardinal JR. Matrix systems, In: Langer RS. and Wise DL. (eds), Medical Applications of Controlled Release, Volume 1, Classes of Systems, CRC Press, Boca Raton, FL, USA, 1984 pp 41-67.*
5. *Durig T, Fassihi R. Mechanistic evaluation of binary effects of magnesium stearate and talc as dissolution retardants at 85% drug loading in an experimental extended release formulation. J Pharm Sci. 1997; 86: 1092-1098.*
6. *Maheshwari M, Ketkar AR, Chauhan B, Patil VB, Paradkar AR. Preparation and characterization of ibuprofen–cetyl alcohol beads by melt solidification technique: effect of variables. Int J Pharm. 2003; 261:57-67.*
7. *Kamble R, Maheshwari M, Paradkar A, Kadam S. Melt Solidification Technique: Incorporation of Higher Wax Content in Ibuprofen Beads. AAPS PharmSciTech. 2004; 5(4): article 61.*
8. *Uhumwangho MU, Okor RS. Modification of drug release from paracetamol granules by melt granulation technique – consideration of release kinetics. Park J. Pharm. Sci. 2006; 19: 27-22.*
9. *Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J .Pharm Sci 1963; 52: 1145-1149.*