IBUPROFEN-GLYCERYL MONOSTEARATE (GMS) BEADS USING MELT SOLIDIFICATION TECHNIQUE: EFFECT OF HLB

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ABSTRACT

The aim of the present study is to elucidate the effect of the HLB of glyceryl monostearate on various pharmaceutical properties of the ibuprofen beads obtained by melt solidification technique. The amount of GMS (15% w/w) and speed of agitation (1200 rpm.) was kept constant to achieve the desired quality beads by melt solidification technique. The beads were spherical in shape exhibit good flowability and satisfactory crushing strength. Drug content of batches was in the range of 82 - 94% w/w. As the HLB of GMS increased the beads surface became rough. The beads were compact with surface pinholes. The FTIR spectra of ibuprofen and ibuprofen- GMS beads showed that there was no interaction between drug and glyceryl monostearate. It showed characteristic peaks of ibuprofen at 1720 cm^{-1} and 2920 cm^{-1}, due to carbonyl and hydroxyl stretching respectively. Scanning electron microscopy (SEM) showed that beads were spherical with smooth surface but after dissolution became rough and porous.

The process yield of various batches was in the range of 83 - 89 % w/w. The beads in the range of -14/+18 # are suitable for capsule filling, hence yield in this range was considered as desired yield. The desired yield of beads from various batches was between 25.64 - 60.32 % w/w. Particle size decreased with increase in HLB of GMS. This is attributed to better emulsification at higher HLB values. Crushing strength was in the range of 75.74 to 126.18 g. The release was extended up to 8 hour and followed Higuchi matrix model. The effect of different HLB of glyceryl monostearate was found to be significant. The beads containing low HLB GMS showed faster drug release than the high HLB GMS.

Keywords: Ibuprofen; glyceryl monostearate; effect of the HLB; melt solidification.

INTRODUCTION

Pharmaceutical processing techniques, which offer freedom from organic solvents, are preferred due to stringent global requirements of quality. Hence many reports are published on techniques such as melt granulation[1,2], melt extrusion[3,4,5], pastillation[6], melt dispersion[7,8,9], and melt solidification[10,11,12]. Lipids, waxes and polyethylene glycols are the most favorable carrier for these techniques. Drug is incorporated in these carriers to achieve controlled release[7, 9, 11], taste masking[13], stability improvement or amorphous form[10]. Design and application of these techniques depend on physicochemical properties of the drug and excipients as well as desired properties of the final product. Wax, a common carrier in various melt techniques, contains wide group of chemicals such as glycerides, fatty acids, fatty alcohols and their esters. These are widely used as release retardant in the design of sustained release beads, tablets, suspensions, implants and microcapsules. The advantages of waxes include good stability at varying pH and moisture levels, well established safe application in human due to its non-swellable and water insoluble nature, minimal effect of food in GIT and no dose dumping[14]. Bees wax, carnauba wax, ceresine, microcrystalline wax, Precirol ATO5 and Gelucire 64/02 were evaluated as waxy carriers for melt processing techniques[7,8,9].

Ibuprofen, α-methyl -4- (2-methylpropyl)-benzene acetic acid, is a non-steriodal anti-inflammatory drug used to treat rheumatoid arthritis, osteoarthritis and mild to moderate pain. Lipophilicity of ibuprofen makes it a suitable candidate for waxy matrices. Paradkar et al.[11] have reported that ibuprofen has very low t_g (<-30 ^{0}C) and remains in liquid state at low temperature, on the basis of which a novel melt solidification technique (MST) was designed.

Melt solidification /melt dispersion technique basically involves emulsification of the molten mass in the aqueous phase followed by its solidification by chilling. Melt dispersion technique reported by Bodmeier et al.[9] and Adeyeye et al.[7] for the development of ibuprofen microspheres involves emulsification of ibuprofen-wax melt at temperature greater than melting point of ibuprofen followed by cooling to room temperature. In this technique, the drug: wax ratios were significantly high from 1:1 to 1:4. The microspheres obtained have drug loading in the range of 15 - 40 %, with particle size between 50 - 300 μm.

Ibuprofen melt has low viscosity and ability to remain in the liquid state for sufficiently longer period of time even at low temperatures. In such cases emulsification can be carried out at temperature well below its melting point. Therefore melt solidification technique to obtain ibuprofen beads was designed where emulsification and solidification of the melt in aqueous phase was carried out at 5 ^{0}C. The beads exhibited slow drug release, which was attributed to formation of melt solidified bonds. Similarly flurbiprofen, due to its melting point (114-117 ^{0}C) above the boiling point of water was never considered as a candidate for melt dispersion technique. But considering its thermal properties similar to ibuprofen, low temperature MST was designed to obtain flurbiprofen waxy beads [12].

For further retardation of drug release and improvement in sphericity cetyl alcohol (CA) was incorporated. CA was selected as a waxy excipient due to its ability to solidify simultaneously with ibuprofen under the processing conditions. The inherent strength of the melt solidified bonds helps to reduce the amount of excipient required to retard the release. Maheshwari et al.[11] reported that the higher processing temperature and concentration of CA affected the sphericity along with the separation of waxy flakes of CA. Similar observations were made by Paradkar et al.[12] in case of flurbiprofen- CA beads where maximum 25 % w/w of CA could be incorporated. It was also observed that the threshold amount of CA above which its release retardant effect is maintained, increases with time. The maximum amount of wax that could be incorporated in low temperature MST depends on the properties of the drug e.g. it was 12.5 % w/w for ibuprofen whereas 25 % w/w for flurbiprofen. But this percentage is significantly low as compared to the melt dispersion technique involving high temperature emulsification. Glyceryl monostearate[15,16] have property to effect the HLB value.

In the present study attempt has been made to elucidate the effect of the HLB of glyceryl monostearate on various pharmaceutical properties of the ibuprofen beads obtained by melt solidification technique. Scanning electron microscopy, Infrared spectroscopy was utilized to characterize the bead.

MATERIALS AND METHODS

Materials

Ibuprofen was kindly supplied by Dr. Reddy's Laboratories (India). Potassium dihydrogen phosphates, ethyl alcohol used were of analytical grade (Merck, India). Glyceryl mono-stearte was obtained from Gattefose S.A., France.

Preparation of Beads

The drug (2 g) and GMS (150 mg) of different HLB (1.5, 3.0, 4.0, 5.0) were melted on a water bath maintained at 100 ⁰C. Homogenous molten mass obtained was poured in 100 ml water maintained at 20 ⁰C using cryostatic bath (Haake Phoenix C25P, Germany), and was stirred continuously using constant speed stirrer with propeller blade (Eurostar power control-visc, IKA Labortecnik, Germany), at 1200 rpm. The beads obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature[17]

Effect of HLB

The process conditions for ibuprofen – Glyceryl monostearate beads were given in Table 1.

Table1: The process conditions for ibuprofen – GMS beads

Batch	Ibuprofen (gm)	GMS (mg)	HLB	Speed (rpm)
GMS-100	2	150	1.5	1200
GMS-101	2	150	3	1200
GMS-102	2	150	4	1200
GMS-103	2	150	5	1200

Evaluation of Beads

Yield and drug content:

Beads were weighed after drying and process yield and desired yield (-14/+18 sieve fraction) were calculated. For determination of drug content, 100 mg beads were triturated and dissolved in 100 ml ethanol by sonication for 30 min. The solution was analyzed spectrophotometrically at 222 nm (JASCO- V500, Japan) after sufficient dilution with phosphate buffer (pH 7.2).

Scanning electron microscopy (SEM):

Beads were coated with a thin gold-palladium layer by sputter coater unit (VG- Micro-tech, UK) and the surface topography was analyzed with a Cambridge Stereo scan S120 scanning electron microscope (SEM, Cambridge, UK) operated at an acceleration voltage of 10 kV.

Infrared spectroscopy (IR):

Fourier-transform infrared (FT-IR) spectra of drug and beads were obtained on JASCO V5300 FT-IR. The pellets were prepared on KBr-press (Spectra Lab, India). The spectra were scanned over the wave number range of 3600 to 400 cm^{-1}.

Crushing strength:

Crushing strength of beads (-14/+18 mesh fraction) was determined using mercury load cell method as described by Jarosz and Parrott (Jarosz, P. J., Parrot, E. J. 1983) on a specially fabricated crushing strength apparatus (Seema Enterprises, Pune, India).

Particle size distribution:

Particle size distribution was studied by sieve analysis technique using Ro-tap sieve shaker (Labtronics, India).

Dissolution studies:

The dissolution studies were performed using USP 26 type II dissolution test apparatus (Electrolab TDT-06P, India). Ibuprofen beads (-14/+18 mesh fraction) equivalent to 300 mg drug were placed in the dissolution vessel containing 900 ml phosphate buffer (pH 7.2) maintained at 370.5 ⁰C and stirred at 100 rpm.[15] Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41, concentration of ibuprofen was determined spectrophotometrically at 222 nm. Analysis of data was done using 'PCP Disso v2.08' software, India[18, 19]

RESULTS AND DISCUSSION

Glyceryl monostearate, a mixture of glyceryl ester of fatty acids is composed of glyceryl monostearate (65%), glyceryl monopalmitate (30%) and glyceryl monomyristate (5%). It has been widely used as an emulsifier in food preparation. This study is an attempt to illustrate the effect of HLB of different grades of GMS of the various properties of the beads.

The amount of GMS (15% w/w) and speed of agitation (1200 rpm.) was kept constant to achieve the desired quality beads by melt solidification technique. The beads obtained by melt solidification technique were spherical in shape with smooth surface. The beads exhibit good flowability and satisfactory crushing strength. Drug content of various batches was in the range of 82 - 94% w/w. The beads obtained were spherical. SEM photographs of ibuprofen- GMS beads containing different grades of GMS are shown in Fig.1. As the HLB of GMS increase the surface became rougher. The beads are compact with surface pinholes.
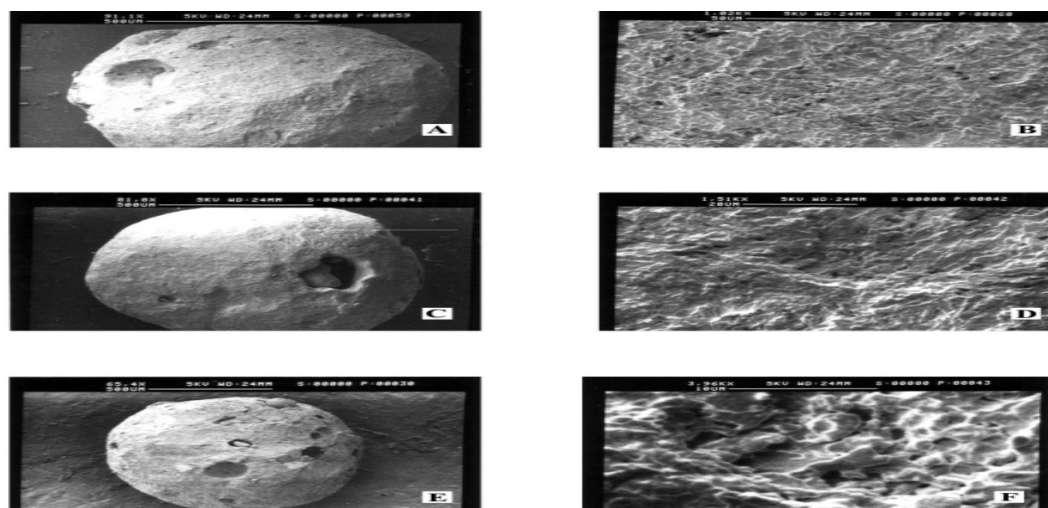

Fig. 1: SEM photographs of IBU–GMS beads with HLB 1.5 at 91.1x (A) and 1020x (B).

HLB 3.0 at 81.1x (C) and 1510x (D) and HLB 5.0 at 65.4x (E) and 3960x (F)

The FTIR spectra of ibuprofen and ibuprofen- GMS beads with different grades of GMS are shown in **Fig. 2.** It showed characteristic peaks of ibuprofen at 1720 cm^{-1} and 2920 cm^{-1}, due to carbonyl and hydroxyl stretching respectively. FTIR revealed that there was no interaction between drug and glyceryl monostearate.
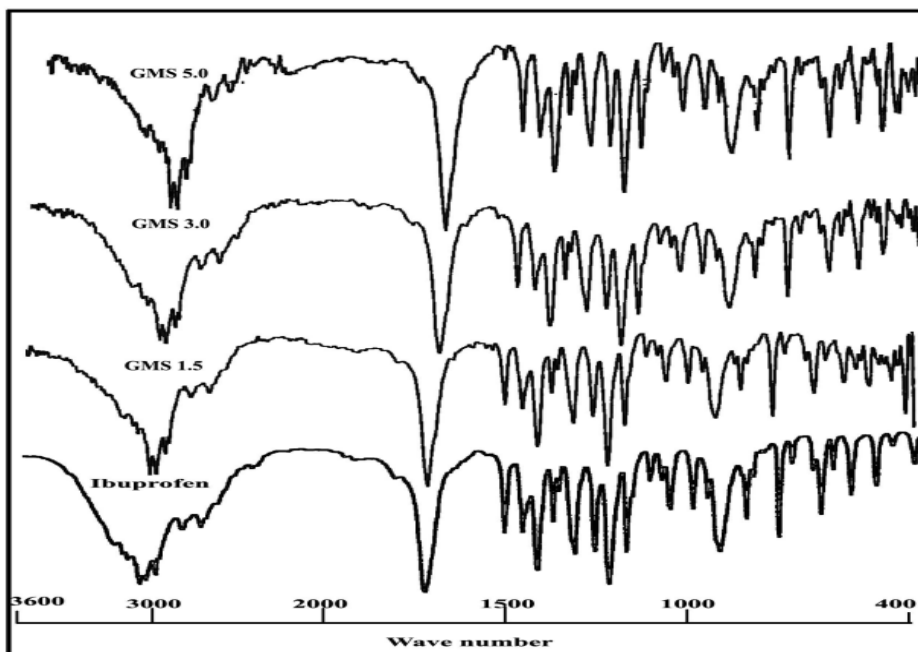

Fig. 2: FTIR spectra of ibuprofen and IBU– GMS beads.

The process yield of various batches was in the range of 83 - 89 % w/w. The beads in the range of -14/+18 # are suitable for capsule filling, hence yield in this range was considered as desired yield. The desired yield of beads from various batches was between 25.64 - 60.32 % w/w.

Crushing strength, which is the force required to crush the beads was in the range of 75.74 to 126.18 g.

Particle size distribution curves for various batches are shown in Fig. 3. Particle size decreased with increase in HLB of GMS. This may be attributed to better emulsification at higher HLB values.
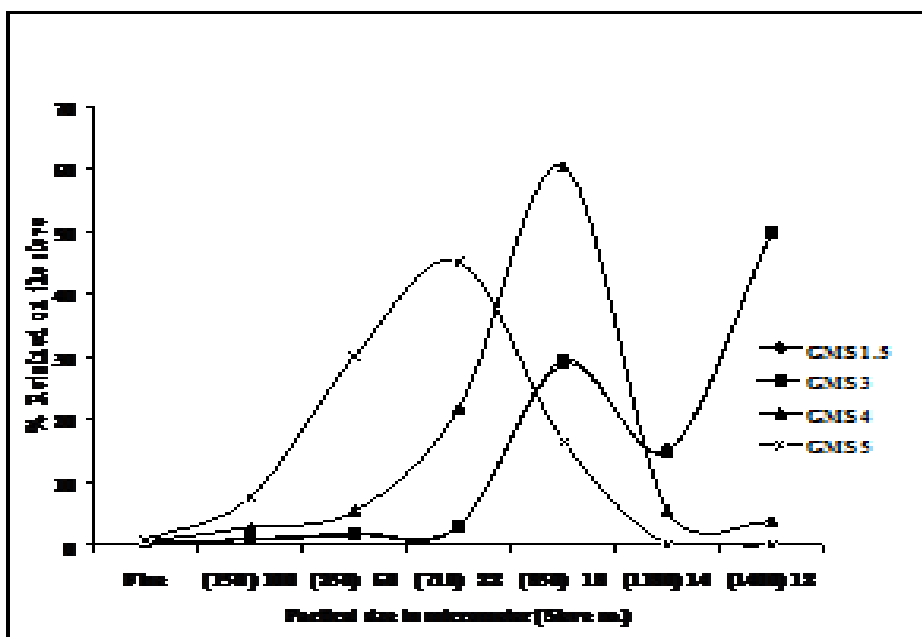

Fig. 3: Particle size distribution curves for IBU -GMS beads obtained with different HLB values.

The release was found to be extended up to 8 hour and followed Higuchi matrix model (Fig. 4). The effect of different HLB of glyceryl monostearate was found to be significant. The beads containing low HLB GMS showed faster drug release than the high HLB GMS. Peh et al. have reported that lipophilic matrix containing GMS retards wetting of the matrix and in turn drug release. This conclusion has been drawn by varying lipophilicity of the binary matrix containing MCC and GMS. But increase in matrix lipophilicity by decrease in HLB in present did not show similar effect on drug release.
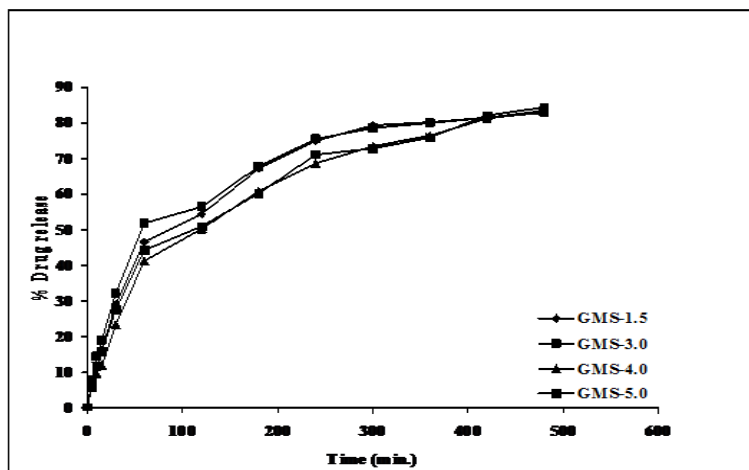

Fig. 4: Dissolution profiles of IBU – GMS beads: Effect of HLB value.

The SEM photograph of the beads containing HLB 3 GMS showed significant erosion and porous structure **(Fig. 5).**
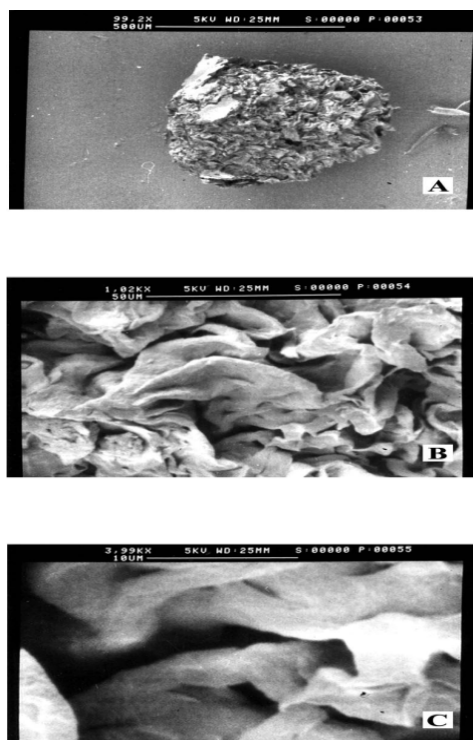

Fig. 5: SEM photographs of IBU – GMS beads after dissolution at 99.2x (A), 1002x (B) and 3990x (C).

CONCLUSION

The ibuprofen – GMS beads by MST were spherical with desired micro-meritic properties. The increased HLB of GMS adversely affected the surface properties. The process has high yield and did not show interaction with additives. The drug release was efficiently sustained.

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