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Review Article

Design and Optimization of Novel Sugar Alcohol Based Extended Release Tablets Prepared by Melt Dispersion Technique

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Abstract

The aim of this study is to prepare novel sorbitol based extended release tablets by melt dispersion method using carbamazepine as a model drug. Carbamazepine was melted along with sugar alcohol to get melt dispersion granules (MGDs) and was characterized by differential scanning calorimetry (DSC), powder X-ray diffractometry (XRD) and solubility study. The physical and chemical parameters of MDGs and tablets were measured while drug release was studied using USP II dissolution apparatus. The release data were subjected to different models to evaluate their release kinetics and mechanisms. Evaluation of MDGs using XRD and DSC indicated that melt dispersion process converted crystalline carbamazepine and sugar alcohol into lower crystallinity with no significant improvement in solubility. The drug release rate was found to be affected by sugar alcohol concentration, particle size of MDGs, the nature of co-excipients, agitation rate and hardness. The kinetics of carbamazepine release from formulation (F3) showed best fit to Higuchi and super case II transport mechanism. It can be concluded that sorbitol is a suitable matrix-forming agent to sustain the release of low soluble drug carbamazepine. Melt dispersion technique using sorbitol is proved to be a promising technique for controlled drug delivery.

Keywords: Carbamazepine; Extended release tablets; Melt dispersion; Sorbitol; Sugar alcohol.
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1. Introduction

In the recent years of development in pharmaceutical dosage forms, more focus is being given for administering drug substances in a more challenging and controlled manner for better therapeutic efficacy. To attain this, various drug delivery systems have been developed or are still under development in treating diseases because of their advantages over other conventional dosage forms [1].

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Drug delivery systems based on the extended release solid dispersion technique are multi-component mixtures of one or more active ingredients in an inert carrier or matrix in solid state. These are prepared either by solvent evaporation method or melting method or a combination of these two methods. In extended release solid dispersion, the dissolution of active ingredient is affected by the presence of one or more other components. Thus more attention has to be paid during the selection of carrier material that will ultimately influence the dissolution characteristics of the dispersed drug [2, 3]. Polymers (Eudragits, Kollidon SR) and waxes (e.g., stearic acid, mono-, di- and tri-glycerides, hydrogenated castor oil, glyceryl behenate, glyceryl monostearate, *etc.*) have been extensively evaluated for sustaining the release of various drugs by solvent evaporation, co-precipitation and melt granulation/extrusion methods [4-7].

Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many non polymeric carriers such as soy, casein and sucrose esters have been evaluated for their use in drug delivery systems [8-10]. Modulation of drug release properties using sugar alcohols from the microcrystalline cellulose based beads prepared by extrusion speronization method has been reported [11].

Sugar alcohols are widely used in pharmaceutical and food industry because of their easy digestible nature, binding ability, abound availability, and chemical compatibility. Generally, sugar alcohol represents good raw materials since they have the advantages of absorbability and low toxicity of the degradation end products. Sugar alcohols such as mannitol and sorbitol have been used extensively in the conventional formulations and orally disintegrating tablets because of their easy use and pleasant taste. However, some anomalous dissolution behaviors of tablets consisting of sugar glass based solid dispersions were reported. In a study, a lipophilic drug like diazepam release rate was modified using four different sugars like trehalose, inulin DP 11, inulin DP 23 and sucrose [12]. However, the use of a sugar alcohol like sorbitol in preparation of extended release solid dispersion by using melt dispersion techniques still remains unexplored. Currently, in pharmaceutical manufacturing operations, hot melt based processes like melt granulation and melt extrusion process using hot melt extruder are widely used due to their simplicity and easy scale up operations. Recently, melt granulation [13] and hot melt extrusion technique [14] have also been successfully employed in the development of extended release formulations.

Therefore, the present study involved

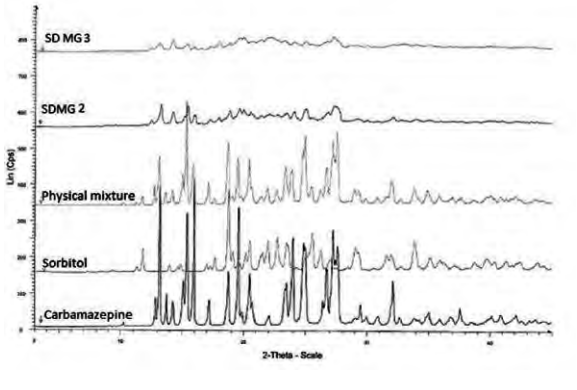

Figure 1. Powder X-ray diffractometry (PXRD) studies of CBZ, sorbitol, physical mixture and SDMG

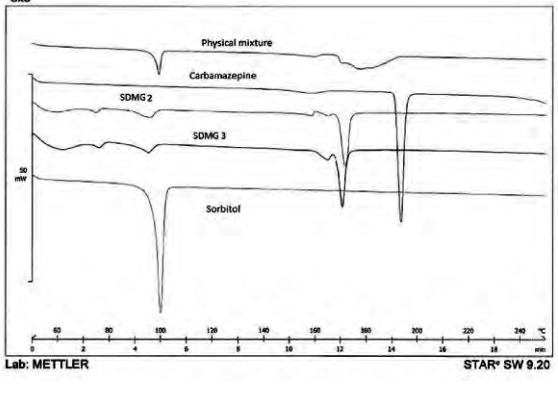

Figure 2. DSC studies of CBZ, sorbitol, physical mixture and SDMG

Table 1. Composition of sugar alcohol based carbamazepine extended release matrix tablet.

Ingredients	Formulation Details											
	F1	F2	F3	F4	F5	F6	F7	F8	F9*	F10#	F11†	F12‡
Carbamazepine	100	100	100	100	100	100	100	100	100	100	100	100
Sorbitol	50	100	200	200	-	200	200	200	200	200	200	200
Lactose monohydrate	250	200	100	100	300	-	100	100	100	100	100	100
Microcrystalline cellulose	-	-	-	-	-	100	-	-	-	-	-	-
Mannitol	-	-	-	-	-	100		-	-	-	-	-
Dicalcium Phosphate	-	-	-	-	-	100		-	-	-	-	-
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Total	404	404	404	404	404	404	404	404	404	404	404	404

*batch containing #20 mesh passed SDMGs; #batch containing #60 mesh passed SDMGs; †batch compressed with hardness of 11-12 kp; ‡batch compressed with hardness of 14-15 kp.

formulation of sugar alcohol based extended release tablets using carbamazepine (CBZ) as a low water-soluble model drug. Sorbitol was used as a meltable binder as well as drug release modifier. Thermal analysis and X-ray diffraction studies were carried out to characterize the solid dispersion for the solid state properties. The matrix tablets of CBZ were prepared by direct compression of granules composed of solid dispersions or physical mixtures of CBZ and sugar alcohol. The release behavior of CBZ from the matrix tablets were studied *in vitro*. The effects of water soluble and water insoluble diluents on the drug release properties of CBZ were also investigated. The effects of hydrodynamics and pH on the release characteristics of the developed formulation were also evaluated. Mechanism of drug release was investigated through dissolution profiling.

2. Materials and methods

2.1. Materials

Carbamazepine (CBZ) was a generous gift from Matrix Laboratories Ltd. (Hyderabad, India). Sorbitol (NeoSorb P60W-Roquette), lactose monohydrate (Pharmatose DCL 21-DMV International), microcrystalline cellulose (Avicel PH 102–FMC biopolymer), dicalcium phosphate (Di-tab, Rhodia) and magnesium stearate (Ferro) were supplied by Matrix Laboratories Ltd. (Hyderabad, India). All other chemicals and solvents were of reagent grade.

2.2. Preparations of melt dispersion granules (MDGs) using sugar alcohol

The melt dispersion granules (MDGs) of CBZ- sugar alcohol (sorbitol) were prepared by the melting method. In melt dispersion method, CBZ and sorbitol were mixed in 1:0.5, 1:1 and 1:2 w/w ratios and were heated

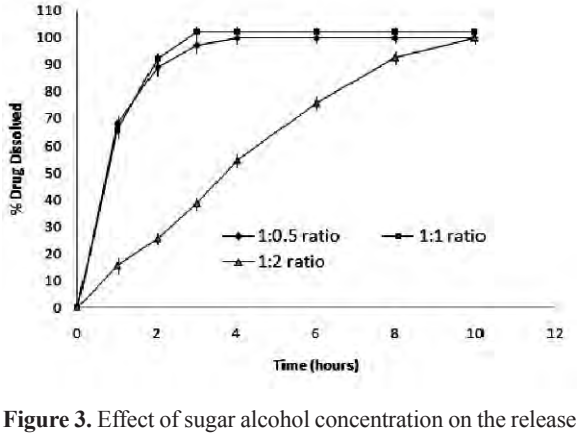

Figure 3. Effect of sugar alcohol concentration on the release profiles of CBZ formulations (F1, F2 and F3)

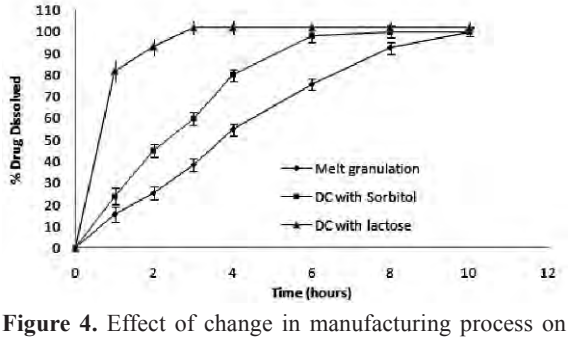

Figure 4. Effect of change in manufacturing process on release profiles of CBZ formulations.

Table 2. Characterization of physical properties of solid dispersion melt granules.

Batch	Evaluation of granules			
	Bulk density (g/cc) (± SD)	Tapped density (g/cc) (± SD)	Carr's index (%) (± SD)	Hausner ratio (± SD)
CBZ	0.758±0.001	0.842±0.003	10.00±0.5	1.11±0.02
Sorbitol	0.610±0.003	0.726±0.005	16.00±1.1	1.19±0.03
PM	0.692±0.004	0.818±0.002	15.40±0.6	1.18±0.02
SDMG1	0.690±0.002	0.800±0.006	13.75±0.7	1.16±0.04
SDMG2	0.645±0.003	0.781±0.004	17.41±0.9	1.21±0.03
SDMG3	0.606±0.005	0.769±0.007	21.20±1.2	1.27±0.02

at a temperature of about 200±10 °C to get a molten mass in a stainless steel vessel using a heating oil bath (Vision Lab Equipments, India). The molten mass was then allowed to cool and solidify at room temperature. The solidified material were allowed to equilibrate for about 48 h and then pulverized in mortar and sized through a #30 mesh ASTM sieve unless otherwise specified.

2.3. Physical characteristics of the granules

The bulk and tapped densities and compressibility of the powder mixture containing pure drug, sugar alcohol, physical mixture of drug and sugar alcohol and MDGs were measured to investigate the physical characteristics of those melted granules for tabletting. Approximately, 30 g of granules were weighed and poured into a 50-ml graduated cylinder. The volume occupied was recorded as bulk volume. The cylinder was then tapped for about 200 times to determine the tap volume. The bulk density (BD) and tapped density (TD) were calculated by dividing the weight of the granules with the corresponding volume. Carr's compressibility index and the Hausner ratio were calculated from the following equations: Compressibility (%)=[(TD-BD)/TD] X100 % and the Hausner ratio = TD/BD.

2.4. Solubility determination

For the determination of solubility of pure CBZ and MDGs, excess material (equivalent to 200 mg of carbamazepine) was placed in contact with 50 ml of purified water in sealed glass volumetric flasks. The flasks were shaken on a vortex shaker (Vortex-T-Scientific Ind, USA) and were maintained at 25 °C for 24 h. An aliquot was withdrawn, filtered through 0.45 µm Whatman filter paper (Whatman Ltd, Middlesex, UK), diluted suitably with water and analyzed by UV spectrophotometer at 288 nm (model UV-1700, UV-Visible spectrophotometer, Shimadzu, Japan).

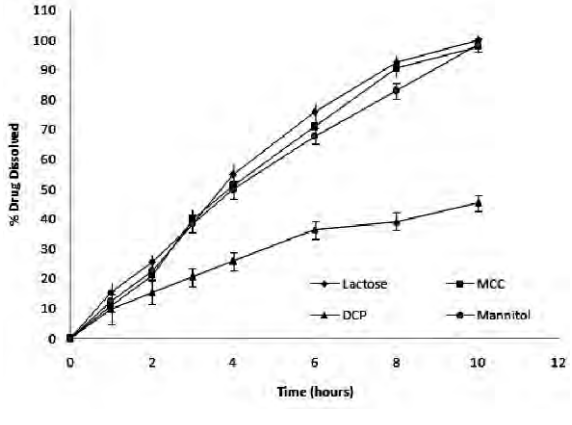

Figure 5. Effect of water soluble and water insoluble fillers on drug release profiles of carbamazepine matrix tablets.

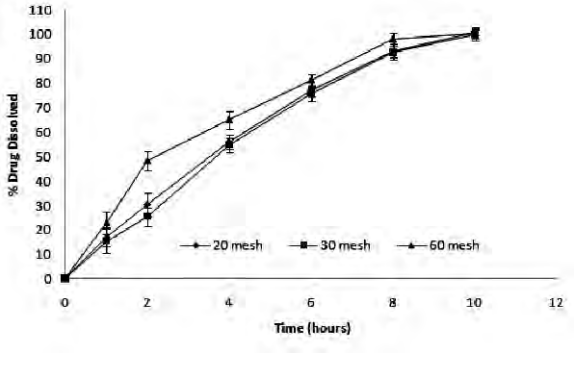

Figure 6. Effect of SDMGs particle size in release properties of carbamazepine matrix tablets

Table 3. Powder X-ray diffractometry (PXRD) characteristic peaks for each polymorphic form of carbamazepine.

Sr.no	Type of Polymorphic form	Characteristic peak value (2θ) in PXRD
1.	Polymorphic form I	7.92 ,9.37,12.28 and 19.99
2.	Polymorphic form II	8.68,13.26,18.56 and 24.54
3.	Polymorphic form III	15.36,19.56,25.00 and 27.47
4.	Polymorphic form IV	14.11,17.89,21.79 and 33.11

2.5. Thermal analysis

Differential scanning calorimetry (DSC) has been one of the commonly used calorimetric methods to characterize the solid state property of the drug in the solid dispersions. Samples of CBZ, sugar alcohol, physical mixtures and MDGs were taken in a flat round bottomed aluminum pans and heated in a temperature range of 50 to 250 °C at a rate of 10 °C per minute with purging of nitrogen (10 ml/min). Indium was used as reference standard in a differential scanning calorimeter (Mettler Toledo, DSC822e, Greifensee, Switzerland).

2.6. Powder X-Ray diffraction studies

Powder X-ray diffraction studies have been used along with DSC to characterize the physical state of the drug in the solid dispersions. X-ray powder diffraction profiles were recorded on x-ray diffractometer (Bruker D8 advance, Germany). The measurement conditions were as follows: Cu kα radiation; voltage, 20 kV; current, 20 mA; receiving slit, 0.1 mm; time constant, 1 second; 2θ range,3 - 40˚; scanning speed 4° 2θ/ min.

2.7. Preparation of tablets

The tablets were prepared by dry blending the MDGs containing drug (equivalent to 100 mg of CBZ) and the diluents followed by direct compression. In each formulation (Table 1), all ingredients, except for magnesium stearate, were screened through a 20-mesh ASTM screen and manually blended for 5 min. Finally, 1% (w/w) magnesium stearate, which was screened through a 60-mesh ASTM screen, was added and mixed for an additional 2 min. All of the formulations of CBZ (equivalent to 100 mg) were compressed into tablets using 8-station, single rotary, D-tooling tablet machine (Kambert Machinery Co.Pvt. Ltd, India) using a 10.3 mm standard concave punches with corresponding die to provide a desirable hardness. The tablets were compressed at different hardness for selected formulation.

2.8. Physical characterization of the designed tablets

The thickness and diameter of 10 tablets of each batch were measured using a vernier caliper (Mitutoyo, Japan). The weight variation was determined by taking weight of 10 tablets using an electronic balance (FX 400, Afcoset, Mumbai, India). Tablet hardness

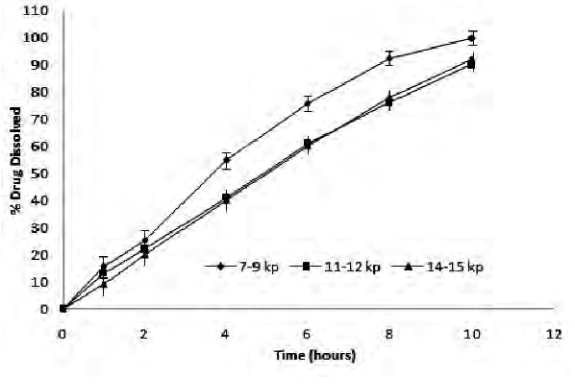

Figure 7. Effect of different compression force on drug release properties of carbamazepine matrix tablets.

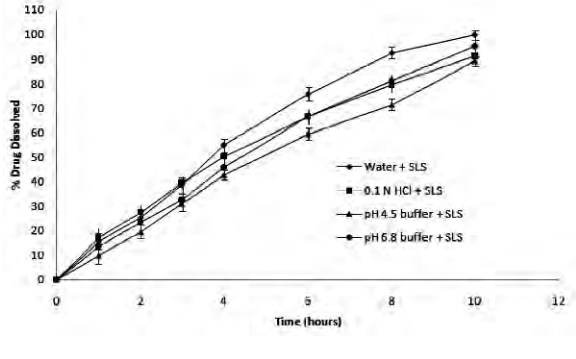

Figure 8. Effect of dissolution medium on drug release properties of carbamazepine matrix tablets.

Table 4. Characterization of granules of carbamazepine.

Batch Code	Physical properties of granules		
	Bulk density (g/cc) (±SD)	Tapped density (g/cc) (±SD)	Carr's index (±SD)
F1	0.587±0.005	0.705±0.006	16.7±0.3
F2	0.504±0.007	0.678±0.005	25.7±0.8
F3	0.672±0.008	0.842±0.004	20.2±0.4
F4	0.578±0.006	0.875±0.003	33.9±1.1
F5	0.448±0.008	0.740±0.005	39.5±1.2
F6	0.601±0.005	0.772±0.006	22.2±0.4
F7	0.682±0.009	0.831±0.007	17.9±0.2
F8	0.693±0.006	0.842±0.008	17.7±0.2
F9	0.659±0.004	0.867±0.005	24.0±0.4
F10	0.501±0.006	0.774±0.006	35.4±0.7

was determined for ten tablets using a tablet hardness tester (Dr. Schleuniger, Germany). Friability was determined by testing ten tablets in a friability tester (EF-1W, Electrolab, Mumbai, India) for 4 min at 25 rpm. The drug content of the manufactured tablets of each batch was determined. For each batch, 10 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in 1% sodium lauryl sulfate (SLS) solution and analyzed after making appropriate dilutions.

2.9. Release rate studies

Release rate for all of the designed formulations were studied using tablet dissolution tester [Dissolution Tester (USP), TDT-08L, Electrolab, Mumbai, India], type II (paddle method) in 900 ml of purified water with 1% SLS as a wetting agent at 37.5±0.5 °C. The agitation speed was set at 50 rpm. At predetermined time intervals, a 10 ml sample was withdrawn and replaced with fresh dissolution media. After appropriate dilution, the samples were analyzed. Cumulative percent of the drug released was calculated and the mean of three tablets was used in data analysis. To study the effect of agitation speed, *in vitro* release studies were also carried out at 100 rpm for selected formulation and keeping the remaining test parameters same as mentioned above. To study the effect of dissolution media, *in vitro* release rate studies of selected formulation was carried out in 900 ml of pH 1.2 (0.1 N HCl solution), pH 4.5 acetate buffer and pH 6.8 phosphate buffer containing 1% SLS as a wetting agent maintaining the agitation speed as 50 rpm and bath temperature at 37.5±0.5 °C.

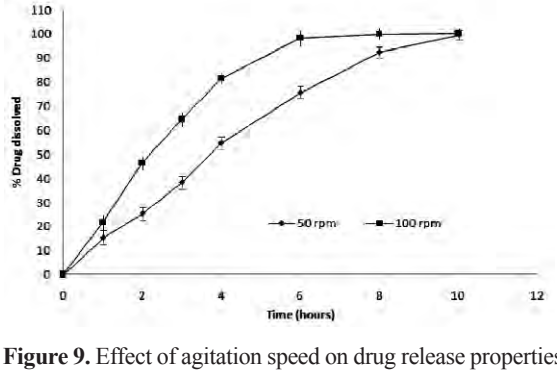

Figure 9. Effect of agitation speed on drug release properties of CBZ formulations

2.10. Drug release kinetics

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Equation 1) as the cumulative amount of drug released vs time, and Higuchi's model (Equation 2) as the cumulative percentage of drug released vs square root of time.

$M_t/M_\infty = K_{0\,t}$ Eq. 1

Where Mt / M∞ is the fraction of drug released at any time "t"; and K0 is the zero-order rate constant.

$M_t/M_\infty = K_H\, t^{1/2}$ Eq. 2

Where K_H is the constant reflecting the design variables of the system and "t" is the time in

Table 5. Characterization of matrix tablets of carbamazepine

Batch Code	Physical properties of carbamazepine matrix tablets (n=10)		
	Assay (%) (± SD)	Hardness (kp)	Thickness (mm) (± SD)
F1	99.1	7-8	4.60 ± 0.04
F2	97.5	7-9	4.64 ± 0.06
F3	98.9	7-9	4.56± 0.03
F4	98.4	8-9	4.30± 0.03
F5	99.3	8-9	4.34± 0.05
F6	99.3	6-9	4.90± 0.04
F7	98.7	7-9	4.61± 0.06
F8	98.7	7-8	4.30± 0.02
F9	99.0	6-8	4.61± 0.06
F10	98.6	6-8	4.70± 0.07
F11	99.2	11-12	4.47± 0.03
F12	99.7	14-15	4.39± 0.03

hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law:

$$(Q_0)^{1/3} - (Q_t)^{1/3} = K_{HC}t \qquad \text{Eq. 3}$$

where Q_t is the amount of drug released in time "t"; Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix Vs time.

The following plots were made: the cumulative percentage of drug release *vs.* time (zero order kinetic model); the cumulative percentage of drug release *vs.* square root of time (higuchi model) and cube root of drug the percentage of the remaining in matrix *vs.* time (hixson-crowell cube root law).

2.11. Mechanism of drug release

To study the release kinetics from sugar alcohol based matrix tablets, the release data were fitted to the well-known exponential equation (power law or Korsmeyer–Peppas equation), which is often used to describe the drug release behavior from polymeric systems [15].

$$M_t/M_\infty = Kt^n \qquad \text{Eq. 4}$$

Where M_t/M_∞ is fraction of drug released at time "t", "k" is the rate constant incorporating the structural and geometric characteristics of the matrix tablets and "n" is the release exponent indicative of the drug release mechanism.

To clarify the release exponent for different batches of matrices, the log value of percentage drug released was plotted against log time for each batch according to the equation 5.

$$\log [M_t/M_\infty] = \log k + n \log t \qquad \text{Eq. 5}$$

In the case of Fickian release (diffusionaly controlled-release), "n" has the limiting values of 0.45 for release from cylinders. Case II transport or relaxation controlled delivery; the exponent n is 0.89 for release from cylinders. The non-Fickian release or anomalous transport of drug occurred when the "n" values are between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to the coupled diffusion/polymer relaxation. Occasionally, values of $n>0.89$ for release from cylinders have been observed, which has been regarded as super case II kinetics [15].

2.12. Release profiles comparison

The drug release profiles were compared using two model-independent methods, mean dissolution time (MDT) and similarity factor (f2) [16].

MDT was calculated from dissolution data

Table 6. Fitting results of experimental dissolution data of CBZ to different release kinetic models.

Batch Code	Regression coefficients (r^2) for various release kinetics models		
	Zero order	Higuchi model	Hixson-Crowell model
F1	0.761	0.925	0.670
F2	0.860	0.952	0.492
F3	0.972	0.988	0.968
F4	0.902	0.958	0.961
F5	0.747	0.997	0.636
F6	0.975	0.991	0.987
F7	0.985	0.996	0.954
F8	0.951	0.989	0.976
F9	0.967	0.993	0.935
F10	0.911	0.976	0.960
F11	0.994	0.990	0.984
F12	0.996	0.991	0.980

using equation 6, and has been used for comparison.

$$MDT = \frac{\sum_{j}^{n} t_j \Delta Q_j}{\sum_{j=1}^{n} \Delta Q_j} \quad \text{Eq. 6}$$

Where "j" is the sample number, "n" the number of time increments considered, t ^$_j$ is the time at midpoint between tj and t_j−1, and ΔQj the additional amount of drug dissolved in the period of time tj and t_j−1.

The similarities between two dissolution profiles were assessed by a pair-wise model independent procedure such as similarity factor (f2):

$$f_2 = 50\ Log\left\{\left[1 + \frac{1}{n\sum_{n=1}^{n=j}(R_t - T_t)^2}\right]^{-0.5} \times 100\right\} \quad \text{Eq. 7}$$

Where "n" is the number of pull points, wt is an optional weight factor, Rt is the reference profile at time point "t", and T_t is the test profile at the same time point; the value of f2 should be between 50 and 100. An f2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases.

3. Results and discussion

3.1. Solubility measurement and physical characterization of MDGs

The saturation solubility of CBZ was found to be 115.6 µg/ml which is in good agreement with the earlier reported value in literature [17]. Solubility of CBZ from the MDGs was also found to be about 115 µg/ml. Saturation solubility study indicated that there was no increase in solubility for MDGs when compared to the pure drug. The physical properties of drug, sugar alcohol, physical mixture and MDGs are shown in Table 2. The compressibility and flow ability of MDGs were found good based on Carr's compressibility index and Hausner ratio.

3.2. Solid state studies

It has been shown that polymorphic changes of the drug substance are important factors that may affect the dissolution rate and bioavailability [18]. Therefore, it is important to study the possible interaction between CBZ and the carrier material in the solid state. CBZ has been found to crystallize as four different anhydrous polymorphs [19, 20]. The four polymorphic form of CBZ were distinguished from each other by PXRD method. The characteristic peaks for all the four polymorphic forms are listed in Table 3. Figure 1 shows the X-ray diffractogram of pure CBZ, sorbitol, physical mixture and

Table 7. Release kinetics parameters and MDT values of designed extended release matrix tablets of carbamazepine.

Batch Code	Korsmeyer-Peppas model				MDT(h)
	r *	n#	K‡ (h n)	t 50 % †	
F1	NA	NA	NA	NA	0.96
F2	NA	NA	NA	NA	0.92
F3	0.984	0.897	14.79	3.89	4.01
F4	0.996	0.841	24.27	2.36	2.88
F5	NA	NA	NA	NA	0.80
F6	0.989	1.158	10.35	3.90	4.19
F7	0.993	0.977	12.30	4.20	4.42
F8	0.993	0.68	9.82	10.95	3.80§
F9	0.999	0.854	16.98	3.54	3.85
F10	0.943	0.749	24.72	2.56	3.17
F11	0.997	0.862	12.62	4.94	4.53
F12	0.998	1.054	9.23	4.97	4.71
F13	0.997	0.766	16.87	4.13	4.04
F14	0.997	1.014	9.977	4.90	4.66
F15	0.994	0.887	13.092	4.53	4.44
F16	0.994	1.004	22.080	2.26	2.48

NA – parameter not determined; # exponential coefficient; *correlation coefficient; ‡ release rate constant; † Time for 50% of the drug release; § MDT for 50% drug release.

MDGs (1:1 %, w/w and 1:2 %, w/w). The diffractogram of CBZ showed sharp characteristics peaks, 2θ at 15.331, 19.530, 24.946 and 27.574. This corresponds to form III polymorph of CBZ [21]. Sorbitol diffractogram showed characteristic high intensity diffraction peaks and can be concluded that commercially available sorbitol exists as polymorphic form B [22]. Physical mixture samples showed diffraction peaks for both CBZ polymrophic form III as well as polymorphic form B of sorbitol. As it is clear from Figure 1, MDGs showed slightly reduced crystallinity compared to the pure components as seen from less intensities and less number for some characteristic peaks.

DSC and XPRD studies are usually combined to determine the polymorphic composition of pharmaceutical powders, when the polymorphs present have different melting points. DSC analysis was employed to evaluate the phase of transformation of CBZ during the formation of MDGs via fusion. DSC thermograms of CBZ polymorph form I show no transformation and melts between 189 and 193 °C [17]. Form II does not melt, but instead a transformation occurs between 135 and 170 °C and the new phase then melts between 188-192 °C. Form III melts and crystallizes to a new form nearly simultaneously between 162 and 175 °C. The new form further melts between 189 -193 °C. Form IV shows melting and partial crystallization to a new form between 178-187 °C and further crystallized to produce a material that then melts between 190-192 °C. The DSC curves of the pure components, physical mixture and the MDGs (1:1, 1:2 weight ratio) are shown in the Figure 2. The thermal profiles of the pure CBZ exhibited one small endothermic peak at 158.01 °C and a major endothermic peak at 191.79 °C with an enthalpy of fusion (ΔH) of 157.1 J/g corresponding to the melting point of CBZ. The DSC curve of sugar alcohol exhibited a sharp endothermic peak at 98.8 °C with an enthalpy of fusion (ΔH) of 196.8 J/g corresponding to the melting point of polymorphic form B of sorbitol. This result is in agreement with a previous study by Sztatisz *et al*. [22].

The DSC study of the physical mixture of carbamazepine and sorbitol (1:2% w/w) included two endotherms where the first peak is attributed to the melting process of the sorbitol and the second broad endothermic

peak is attributed to the melting process of the drug. In case of the MDGs, a small endothermic peak observed at 75 °C could be due to the presence of amorphous sorbitol where as endothermic peak at 95 °C could be due to the presence of crystalline form B sorbitol [22]. The DSC thermograms of the MDGs also showed two small endothermic peaks around 155 °C, 164 °C and one sharp endothermic peak at 170 °C corresponding to the melting form of form III. One interesting finding from the DSC thermogram is that in the MDGs, a stable polymorphic form III of CBZ was presented, and it is not further melted to crystalline polymorphic form I as indicated by the melting point where as the literature study reveals that all other three polymorphic forms II, III and IV will be melted and recrystallized to polymorphic form I during the DSC analysis.

3.3. Physical characterization of granules and tablets

The granules for matrix tablet were prepared according to the formula given in Table 1 and characterized with respect to bulk density, tapped density and Carr's index (Table 4).

The physical and chemical properties like tablet hardness, thickness and drug content uniformity of all tablets were found to be satisfactory and reproducible as observed from the data in Table 5. The thickness of the tablets varied depending on the nature of material used and the compression force. Tablet hardness was found to be good (between 6.0-15.0 kp) depending on the compression force applied and friability was less than 1% (w/w) (data not shown). The manufactured tablets showed low weight variation (less than 3%) (data not shown) and a high degree of drug content uniformity indicated that the melt dispersion method used is an acceptable method for preparing good quality matrix tablets of carbamazepine.

3.4. in vitro drug release analysis

in vitro drug release from matrix systems depends on several factors, such as the manufacturing method, concentration of the polymer, drug solubility, drug load, pH of the dissolution medium, agitation rate and the nature of excipients [23-25].

3.5. Effect of sugar alcohol concentration

The effect of sugar alcohol concentration on drug release characteristics was studied by varying the drug to sugar alcohol weight ratio in the melt dispersion process. The drug release profile from formulations F1, F2 and F3 is shown in Figure 3. It can be concluded that drug to sugar alcohol weight ratio has a significant effect on dissolution characteristics from the matrix tablets. More than 80% of the drug was released within 2 h for the formulations F1 and F2 containing melt granules of 1:0.5 and 1:1 weight ratio of drug to sugar alcohol, respectively. For instance, Formulation F1 and F2 showed similar drug release profiles as indicated by higher f2 value (79.7). Formulation (F3) with higher concentration of drug to sugar alcohol weight ratio (1:2) showed a significantly extended drug release where about 80% of the drug was released in about 8 h. The release rate decreased with the increase in sugar alcohol proportion. The calculated MDT value was found to be 4.01 h as the sugar alcohol proportion increased to 1:2 weight ratio. The f2 factor value was found to be 12.35 between the Formulations (F2 Vs F3), indicating that the release profiles were significantly different.

These results suggested that the amount of sugar alcohol and consequently the extent of dispersion between drug and sugar alcohol was the parameter that most affected the CBZ release. The 1:0.5 and 1:1 drug–sugar alcohol ratio was not suitable to control the drug release, showing substantial burst effect. The faster drug release from the F1 and F2 formulations could be attributed that the drug

is not uniformly distributed in the MDGs and the free drug is easily available for the dissolution. As the sugar alcohol content decreased, the drug release rate increased due to the increase in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug) and decrease in the tortuosity (the length of the diffusion path of the solute [26, 27]. Extended release from the 1:2 MDGs formulation might be explained on the basis that CBZ is more completely dispersed in the MDGs compared to the F1 and F2 formulations, slower dissolution rate from the matrix tablets and also because of the low solubility of CBZ.

3.6. Effect of manufacturing process on drug release

The effect of manufacturing process on drug release characteristic from the formulation was investigated by preparing tablet by direct compression as well as melt dispersion method.

For the comparison purpose, one formulation (F5) with direct compression process using lactose as filler was prepared and evaluated for drug release properties. As shown in Figure 4, formulation (F5) showed a faster drug release (more than 80% drug release within one hour). Formulation prepared using melt dispersion (F3) method showed a slower and extended dissolution property where about 80% drug release was achieved after 8 h and the MDT observed was 4.01 h. Formulation prepared by direct compression process using sorbitol (F4) showed an intermediate dissolution profile between formulations F3 and F5 where about 80% of the drug was released in about 4 h. When the drug release profile was compared between the formulations prepared by direct compression process and melt dispersion process, a significant difference in drug release profile was observed as indicated by the increased MDT values (2.88 h to 4.01 h) and lower F2 values (34.7). A significant difference in drug release profiles was observed for F4 and F5 formulations as indicated by lower f2 value (17.8). Formulation prepared using lactose was found to disintegrate after one h of the dissolution process and rapidly released the drug content, whereas formulation prepared using sugar alcohol was found to dissolve by slower erosion. An improved control of drug release rate was observed for formulation prepared by melt dispersion process compared to direct compression process using lactose as well as sorbitol as diluents. Extended release from the melt dispersion formulation could be attributed to the formation of a more uniform and, therefore, more effective coating of the CBZ drug particles by sugar alcohol in the tablets prepared by melt dispersion technique than in those made by direct compression. The reason for this phenomenon can be explained by the penetration of the dissolution medium into the melt dispersion formulation, which is low compared with matrices prepared by physical mixtures, and hence, the dissolution and release of the drug occurs at a slower rate. Similar results were reported by Abdelkader *et al*. [28] when baclofen matrix tablets were prepared by melt granulation method using hydrogenated castor oil showed delayed drug release properties than matrix tablets prepared by wet granulation method using eudraigt rs 100 and eudragit l 100. Anomalous dissolution behavior of tablets prepared from sugar glass based solid dispersions for diazepam were reported by Vam drooge *et al*.[12] where dissolution of diazepam was found to be slower when the fast dissolving sugar carriers like sucrose and trehalose were used with high drug loads.

3.7. Effect of filler type on drug release

The effect of diluents type [water soluble (lactose and mannitol) or water insoluble (microcrystalline cellulose and dicalcium phosphate)] on *in vitro* drug release profile from the matrix tablet prepared using MDGs

of 1:2 drug to sugar alcohol weight ratio with hardness of 7-9 kp are shown in Figure 5. Formulations prepared using lactose (F3), microcrystalline cellulose (F6) and mannitol (F7) as filler were found to have complete drug release (more than 85% drug release at 10 h). Significant change in release rate and MDT were observed for formulation F8 compared to formulation (F3) (Table 7). Formulation prepared using dicalcium phosphate (F8) as a filler was found to have incomplete drug release (only 45% of drug at 10 h compared to more than 85% drug release at 10 h for other diluents). The drug release profiles were also analyzed for the similarity factor (f2) values for assessment of statistical difference or similarity between the release profiles. The f2 factor value was observed to be 25.6 between lactose and DCP formulations, indicating the significant difference between the release profiles, whereas the f2 factor values were found to be 61.9 between lactose and mannitol formulations, 70.5 between lactose and MCC formulations and 71.8 between mannitol and MCC formulations, indicating no significant difference between the release profiles of lactose, mannitol and MCC formulations. The calculated MDT values using equation 6, were found to be 4.01 h, 4.19 h, and 4.42 h, respectively, for the formulations prepared using lactose, MCC and mannitol as fillers indicated no significant difference in MDT. On the other hand, the calculated MDT for DCP (F8) formulations was found to be 12.22 by using N value derived from Korsmeyer-peppas equation as reported earlier indicated significant difference in drug release rate.

3.8. Effect of particle size on drug release

The effect of particle size on dissolution was studied using formulation containing MDGs 1:2 of drug to sugar alcohol weight ratio. MDGs were passed through #20, #30, and #60 mesh ASTM screen and the fractions were collected, separately. Three separate formulations were prepared using these different particle fractions using lactose as filler having hardness of 7-9 kp. The *in vitro* drug release profile in 900 ml of purified water with 1% SLS is shown in Figure 6. No significant change in drug release profile was observed for formulations having #20 mesh (F9) and #30 mesh (F3) fractions of MDGs as indicated by the higher f2 value of 79.8 and comparable MDT values of 4.01 h and 3.85 h for F3 and F9 formulations, respectively. A significant change in drug release profile was observed for formulation having #60 mesh MDGs (F10) as compared to F 3 formulation containing #30 mesh fractions of MDGs as indicated by the lower f2 value of 47.6 and lower MDT values of 4.01 h and 3.17 h for F3 and F10 formulations, respectively. The faster drug release rate from lower particle size (#60 mesh) formulations (F 10) was confirmed by the higher K values of 24.72% h−0.749 and the t50% value of 2.56 h as compared to the K value of 14.79% h−0.897 and the t50% value of 3.89 h for the formulation with particle size of #30 mesh fractions (F3). The effect of particle size on the release rate was found to be more pronounced at lower particle size (#60 mesh) than at higher particle size (#20 and #30 mesh).The increase in the drug release rate in formulation having #60 mesh fractions of MDGs could be attributed to the reduction of particles size which could lead to the higher surface area available for dissolution. Similar results were obtained by other researchers, who studied the effect of particle size on drug release from solid dispersion matrix systems [29, 30].

3.9. Effect of compression force on drug release

The effect of compression force on the hardness, apparent density, and porosity of the tablet is reported in the literature by several authors [31-34]. It was also found that an increase in the compression force increases the hardness and the apparent density of the tablet,

thereby reducing the matrix porosity in the tablet [32]. The effect of compression force on the drug release was studied by preparing tablets using MDGs of 1: 2 weight ratios of drug to sugar alcohol and using lactose as filler but with different compression forces to get tablets with different hardness levels, 7-9 kp, 11-12 kp and 14-15 kp. The effects of compression force on the drug release from prepared CBZ formulations are shown in Figure 7. The release of the drug from formulations prepared with less compression force (F3; hardness 7-9 kp) was found to faster with K values of 14.79 % $h^{-0.897}$ than the release of the drug from formulations prepared with higher compression forces (K values are 12.62 % $h^{-0.862}$ and 9.23% $h^{-1.054}$ for hardness 11-12 kp [F11] and 14-15 kp [F12], respectively). The calculated MDT values were found to be 4.01 h, 4.53 h and 4.71 h for hardness levels of 7-9 kp, 11-12 kp and 14-15 kp, respectively. As shown in Figure 7, a significant difference was observed in the release profiles of tablets compressed with lower hardness (7-9 kp) as indicated by lower f2 value (46.9) when compared with higher hardness formulation (F12). Release profiles from formulation (F11 and F12) were comparable as indicated by higher f2 value (80.6). This could be because of a significant decrease in the porosity of the matrix with increase in hardness from 7-9 kp to 11-12 kp, but beyond hardness level of 11 kp there was no significant change in the porosity of the matrix.

3.10. Effect of dissolution medium on drug release

The effect of dissolution medium (purified water, pH 1.2, pH 4.5 acetate buffer and pH 6.8 phosphate buffer with 1% SLS) on the drug release from selected formulation (F3) compressed with hardness of 7.0-9.0 kp is shown in Figure 8. The drug release was fastest in purified water with 1% SLS as indicated by the higher K value of 14.79% $h^{-0.897}$ and lower t50% 3.89 h. The drug release was slowest in pH 4.5 acetate buffer with a K value of 9.98% $h^{-1.014}$ and t50% 4.90 h. The f2 factor value of 44.69- further demonstrated that the drug release was significantly lower in pH 4.5 acetate buffer compared to the release in purified water with 1% SLS. The drug release profile from pH 1.2 (0.1 N HCl) and pH 6.8 phosphate buffer were comparable to drug release profile from purified water with 1% SLS based on higher f2 value of 57.88 and 56.04, respectively. The calculated MDT values were found to be 4.01 h, 4.04 h, 4.66 h, and 4.44 h, respectively, for the release profiles of purified water, pH 1.2, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The faster release in purified water with 1% SLS could be attributed due to the higher solubility of CBZ in the particular medium. Lee *et al* [35] reported a slightly higher solubility of CBZ in dissolution medium of purified water with SLS compared to 0.1 N HCl, pH 4.0 and pH 6.8 buffer containing 1% SLS. Solubility of CBZ in 0.1 N HCl, pH 4.5 and pH 6.8 buffer containing 1% SLS were comparable.

3.11. Effect of agitation speed on drug release

It is known that the drug release rate from the delivery system shall be influenced by the factors that influence dissolution such as the thickness of the diffusion boundary layer if it is controlled by the dissolution of drug. The aqueous diffusion boundary layer around the matrix offers significant resistance to the dissolution of poorly soluble drug. The thickness of the aqueous diffusion boundary layer is affected by the rate of agitation speeds in the dissolution medium: the higher the agitation rate, the thinner the aqueous diffusion boundary layer. If the release of CBZ is solely controlled by its dissolution in the release medium, then increasing the agitation rate should accelerate the release of CBZ. The effect of agitation speed, 50 and

100 rpm, on the *in vitro* drug release profiles of CBZ from selected formulation (F3) in 900 ml of purified water with 1% SLS is shown in Figure 9.

A significant difference in drug release rate was observed when agitation speed was increased from 50 rpm to 100 rpm as indicated by the decrease in MDT values (from 4.01 h for 50 rpm to 2.48 h for 100 rpm) as well as lower f2 value (34.71). Similarly, the drug release rate was found to be increased significantly with increase in agitation speed. The value of K increased from 14.79 % $h^{-0.897}$ to 22.08 % $h^{-1.004}$ and the value of t50% decreased from 3.89 to 2.26 h as the agitation speed increased from 50 rpm to 100 rpm. The increase in drug release rate with increase in agitation speed in formulation was due to the increase in the attrition of matrix structure. Release rate of diclofenac sodium from lipophilic matrix tablets in pH 5.8 phosphate buffer solution was increased as the rotational speed was increased [36]. Similar results were reported for the release increment of zidovudine from HPMC matrix tablet with increasing rotational speed [37].

3.12. Release kinetics and mechanism of dissolution

To analyze the mechanism of drug release from the sugar alcohol based CBZ matrix tablets, the dissolution data were fitted to various kinetic models, the release kinetic parameters and the fitting ability (correlation coefficient, r) are listed in Table 6. It can be observed from the results that the release rate data of CBZ matrix tablets (F1-F10 formulations) fitted well to the Higuchi's square root release kinetics, as indicated by highest value of r2, while that of F11 and F 12 formulations (compressed into hardness of 11-12 kp and 14-15 kp) were fitted well into zero- order release kinetics.

The release mechanism and kinetics of the release profiles were analyzed by Korsmeyer–Peppas model, (Equ. 4), up to 60% release [15, 38]. The values of K, n, t 50% (time for 50% of drug release) and r (correlation coefficient) obtained for various formulations are listed in Table 7. Release kinetic analysis using Korsmeyer-Peppas model were not performed for the formulations F1, F2 and F5 where, more than 70% of the drug was already released during the first hour of the experiment (Figure 3 and 4). As observed from the table, the values of correlation coefficient (r2) for all other formulations were high enough to evaluate the drug dissolution behavior by Equation 5. The values of "n" for formulations containing MDGs of 1:2 weight ratio of drug to sugar alcohol with lactose (F3), microcrystalline cellulose (F6) and mannitol (F7) as fillers in 1% SLS solution were found to be 0.897, 1.094 and 0.977, respectively, indicated that the drug release was Super Case II release mechanism and furthermore together with the good fitting of the zero-order model indicate significant contribution of erosion. The "n" value of 0.68 for F8 formulation (DCP) indicated that the release mechanism was non-Fickian or anomalous release ($0.45>n<0.89$). It can be inferred that the release was dependent mainly on drug diffusion. This finding agrees with those of Liu *et al*. [39] and El-Shanawany [40] who reported that DCP was insoluble and non-swelling filler. Thus, the tablets will remain intact throughout the dissolution process and the drug will be released by diffusion through small inter- and intra-particle spaces. When lactose or MCC or mannitol was used as filler, water was absorbed into the tablet through capillaries, leading to swelling and formation of new cracks and channels from which a further amount of the drug was dissolved and released with no disintegration of the tablet.

4. Conclusion

A new type of non-polymeric sugar alcohol

matrix that can be used in controlled release applications has been developed using melt-based processing techniques. MDGs of carbamazepine were obtained by melt dispersion method. Solid state characterization of the MDGs showed reduced drug crystallinity. No significant increase in solubility of CBZ was observed for MDGs. Matrix tablets prepared from MDGs were more effective than those from physical mixtures in controlling the drug release rate. However, it was possible to adjust the release characteristics by employment of other ingredients like water soluble and water insoluble diluents. Release rate of the drug from the matrix tablets was dependent on the sugar alcohol concentration, particle size of the MDGs and the compression force used. Based on the analysis of release kinetic properties, the predominant release mechanism from the matrix tablets prepared was found to be erosion mechanism. This study showed that sugar alcohol can be utilized as a suitable matrix-forming agent to modulate the release of a poorly water-soluble drug CBZ. The major advantages of these novel sugar alcohol based matrix systems are as follows: (i) simple and cost effective (ii) ease of production (especially at industrial scale using hot melt extruder) (iii) applicability to different types of drugs; (iv) biodegradability.

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