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Comparative evaluation of porous silica based carriers for lipids and liquid drug formulations

Abstract: Conversion of liquid and semisolid lipids into free flowing powders is an advantageous technique, as the carriers display high surface area, strong adsorption capacity, ease of processing, and ability to generate lipid loaded free flowing powders which can be converted to solid dosage forms like tablets and capsules. A combination of density, adsorption capacity and desorption is found to be of importance in the selection of the right adsorbent. Adsorbents like magnesium aluminium silicates (MAS), granulated fumed silica (GFS) and mesoporous silica gel (MSG) were characterized by flow property measurements, particle size, scanning electron microscopy (SEM) and pore structure by mercury (Hg) intrusion study. SEM results reveal adsorbent morphology, whereas an intrusion-extrusion study reveal pore size distributions. Tablets and capsules of oil loaded adsorbents were prepared by conventional methods. Oil loaded adsorbents were evaluated for the ability to convert oil into powder, easy of processing into tablets and capsules, and release of the loaded oil (Vitamin E) or active (Glyburide). All adsorbents possess good flow property while MSG has higher density than GFS and MAS. This helps to deliver maximum active per unit volume. A wider pore size distribution of MAS was observed in comparison to MSG and GFS. MAS exhibited poor oil release from powder and its formulations, whereas GFS demonstrated closely similar release to MSG. Maximum 70% oil loaded MSG can be delivered in tablet dosage form and MSG can deliver the highest amount in limited volume capsules due to its high density. Hence, lower density and poor oil release from MAS limit its applications in solid oral drug delivery, while both MSG and GFS proved to be suitable.

Keywords: Drug delivery systems, Dissolution, Adsorption, Desorption, Self-emulsifying, Mesoporous silica gel, Liquisolid, Oil, SEDDS, Silicates, SMEDDS

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1 Introduction

The oral route of drug administration is preferred extensively by both patients and physicians. Patients favor the oral route due to reduced need for hospitalization, medical and nursing aid, easy of administration, etc. [1] while according to physicians, oral administration of drugs show better activity and tolerability [2]. According to pharmaceutical formulators, oral solid dosage forms can be produced in a non-sterile environment and the process, equipment and technology are well defined and established, after more than 100 years of research. However, for absorption of a drug, it must be dissolved prior to permeation through the gastrointestinal tract (GIT) membrane. As a result, dissolution and permeation are the rate limiting steps for bioavailability of orally administered drugs. According to Tang *et al.*, approximately 40% of the drugs are poorly water-soluble [3] and 70% of the new chemical entities possess water solubility issues [4, 5], which may result in low oral bioavailability. Hence, achieving oral bioavailability for poorly water-soluble drugs is a major challenge for formulators in the future.

Dissolution of poorly water-soluble drugs can be improved by different techniques such as increasing the surface area (micronisation) [6], improving drug wettability (co-grinding) [7], as well as formulating the drug using inclusion complexes [8], solid dispersions [9] and lipid-based formulations [10]. These delivery systems have

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been evaluated by various researchers with different success rates. Among them, lipid based drug delivery systems like simple oil solutions, self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) are often used for delivery of poorly water-soluble drugs due to improved biocompatibility as opposed to alternate drug delivery systems where excipients may create compatibility issues in addition to higher solubility of the drug in the GIT and increased bioavailability of the poorly water-soluble drug [11]. Furthermore, lipid-based formulations can also be used to protect moisture sensitive drugs from hydrolysis and to improve enzymatic stability [12]. Furthermore, Cristiansen *et al.* observed that food effects of cinnarizine can be avoided by formulating the drug in SMEDDS [13]. However, most of the lipids are liquids or semisolids and are difficult to formulate in solid dosage forms. They are typically delivered through soft or hard gelatin capsules as a solid oral dosage form. Some of the examples of lipid delivery systems available in the market include Neoral® (cyclosporine A), Norvir® (ritonavir), Fortovase® (saquinavir) soft gelatin capsules and Solufen® (ibuprofen) hard gelatin capsules [14, 15].

Some limitations of using soft gelatin capsules are difficulty filling these capsules with highly viscous lipids which inceases the cost of the process. In addition, low molecular weight polar molecules present in lipid formulations may penetrate and plasticize the gelatin capsule shells, thereby restricting the concentration of propylene glycol and related co-solvents that can be used in capsule fillings, resulting in reduced efficacy of formulation [16, 17].

One way to address this issue is to convert these liquid and semisolid lipids into free flowing powders and design robust solid dosage forms. Adsorption on a solid carrier, spray drying, and co-mixing with polyethylene glycols are some of the reported methods for converting liquid formulations to a solid form [18]. Adsorption on solid carriers is an advantageous technique, as the carriers display high surface area, strong adsorption capacity, ease of processing, and ability to generate lipid loaded free flowing powders which can be converted to solid dosage forms like tablets and capsules. Solid adsorbents are increasingly gaining the attention of formulators for the design of lipid based oral drug delivery systems [19]. Use of microcrystalline cellulose as an adsorbent was attempted by Qi *et al.* for the Celastrol SMEDDS formulation [20]. Kima *et al.* used silicone dioxide as adsorbent for the solid SMEDDS formulations of clopidogrel napadisilate [21]. Some of the other examples include cellulose derivatives, porous silica, talc, Kaolin, Isomaltose etc. Among them, various silicates like mesoporous silica gel (MSG), granulated fumed silica (GFS) and magnesium aluminium silicates (MAS) are used widely for oral delivery of oils and lipid formulations. However, an optimized adsorbent is one which has maximum adsorption capacity and maintains good flow property even after adsorption of oils/lipids. It should be easy to process into solid dosage forms and compatible with other excipients to help ensure maximum stability. Additionally, it should desorb the adsorbed drugs as well as excipients in GIT to achieve desired bioavailability. As a result, we evaluated different types of silica based adsorbents to determine their suitability as solid absorbents.

2 Experimental

2.1 Materials

The silica gel carriers used in this study, namely Syloid® XDP mesoporous silica gels (MSG) and SYLOID® 244FP silica, were obtained from Grace GmbH & Co.KG (Worms, Germany). Sample of Aeroperl® 300Pharma granulated fumed silica (GFS) was obtained from Evonik Industries (Germany), Fujicalin® Dicalcium phosphate (DCP) and Neusilin® US2 magnesium aluminum silicate (MAS) were obtained from Gangwal Chemicals India. Glyburide and crosscarmellose sodium were supplied by Avian International Ltd. Magnesium stearate USP/NF and talc were obtained from Nitika Chemicals Ltd., India. Isomaltose was received from Beneo-palatinit GmbH (Germany). Microcrystalline cellulose (MCC) and alpha Vitamin E were supplied by Reliance Cellulose Ltd. and Sigma-Aldrich, respectively. Capryol 90™, Transcutol® HP, Labrasol® , Labrafac® PG and Labrafil® M1944CS were obtained as gift samples from Gattefosse, France. Capmul® MCM EP and Captex® 355 EP/NF were supplied by Abitec Corporation. Cremophor® EL was supplied by BASF GmbH, Germany. All other oils used in this study were obtained from local sources. Tween 80, Tween 20 and polyvinylpyrrolidone K-30 were supplied by Sisco Research Labs Pvt Ltd., Mumbai. All the other materials and reagents were of analytical grade.

2.2 Characterization of adsorbent carriers

Particle size was determined by laser light scattering principle using a Malvern® Mastersizer® 2000 with the dispersion unit Hydro™ 2000 G. The surface characteristics of adsorbents were determined by SEM analysis (JEOL Com-

pany, Model JSM 6380). Hg intrusion-extrusion technique was used for studying the pore volume and pore diameter, while the surface area of MSG was obtained using the single point gas adsorption BET (Brunauer, Emmett and Teller) method (Micromeritics, Flowsorb 2300) at –196°C under relative nitrogen pressure (P/P_0) of 0.3 and compared with the reported values of GFS and MAS. Tapped density (TD) and bulk density (BD) were determined using procedure mentioned in chapter 616, USP 30 NF 25. Angle of repose (AR), % compressibility index (CI), Hausner ratio (HR) for all powders were measured according to procedure and formula mentioned in chapter 1174, USP 30 NF 25.

2.3 Determination of maximum oil/lipid loading capacity

The solid adsorbent (2g) was placed in a beaker (at 23°C, 60% relative humidity, RH), and oil was added drop wise from a burette, with constant stirring until a dry paste-like mass was obtained. The volume of oil consumed was noted, and used in the below equation to calculate the maximum oil adsorption capacity per 100g of solid carrier:

$$\text{Volume of oil consumed (mL)} \times \text{Specific gravity of oil (g/mL)} \times 100$$

Similarly vitamin E (alpha-Tocopherol) was mixed separately with different silica-based carriers in various proportions (Carrier:Vitamin E) such as 1:0, 1:0.25, 1:0.5, 1:1 and 1:1.5 in the above described manner. The prepared mixtures were kept for 24h to allow the loaded mixture to reach a final volume and ensure complete adsorption of oils in pores of carrier. Flow properties of oil loaded carriers were determined as described in the characterization procedure.

2.4 The effect of humidity on oil (Vitamin E) loading

Humidity of 90% RH and 24°C was maintained in desiccators with saturated potassium chloride [22]. The humidity values were monitored with a hygrometer. Both MSG and calcined silica samples were kept at 90% RH and 24°C for 48h and used for oil loading at 1:1 ratio. Oil desorption and oil releases were determined using in house procedure as described below.

2.5 Determination of oil desorption

The free flowing oil loaded carrier was dispersed in water in the ratio of 1:3 for 30min on Spinix vortex shaker (Tarsons) and centrifuged (Thermo Scientific) at 5000rpm for 10min. The supernatant was transferred to a Petri plate and kept in an oven at 80°C to evaporate water. The amount of oil desorbed from solid material was calculated gravimetrically. Similarly, the effect of humidity, pore structure, surfactant (3% Tween 80) in dissolution media and calcinations of MSG on oil desorption were also studied using the same procedure:

$$\text{(Amount of Oil desorbed in desorption media/Theoretical amount of loaded oil)} \times 100$$

2.6 Oil (Vitamin E) release study

Oil loaded carrier equivalent to 250 mg of Vitamin E was weighed and subjected to dissolution study in 1% sodium lauryl sulphate (SLS) in water using USP apparatus II at 75rpm, 37°C. An aliquot of 5mL was withdrawn after 45min, filtered through Acrodisc® 25mm syringe filter with 0.45µ Nylon membrane and analyzed using HPLC (Waters Acquity H-class) using a Grace® Vision HT® high load C18 column, Rocket Format, (53×7mm, 3µm) as the stationary phase and Acetonitrile: Methanol: H_2O (85:10:5) as the mobile phase at a flow rate of 1.5mL/min. Injection volume was 20 µl and wavelength of analysis was 294nm.

2.7 Development of solid oil/lipid and SEDDS using MSG as adsorbent

2.7.1 Preparation of tablet and capsule as dosage form for oil and lipid delivery

The tablets equivalent to 100mg of Vitamin E were prepared via direct compression (DC) after mixing Vitamin E loaded adsorbent carrier with different amounts of MCC (filler), pregelatinised starch (binder), SYLOID® 244 FP silica (glidant), and magnesium stearate (lubricant). A homogenous blend was passed through a 425µm nominal aperture sieve and then directly compressed into tablets using a rotary tablet machine with a 12mm concave punch (Eliza Press 200, Gujarat, India) at 20KN force. Obtained tablets were evaluated for weight variation, hardness, disintegration time by tablet disintegration tester, LABINDIA, DT 1000 (water, 900mL as media), ejection force by Eliza Press 200 and friability by Electrolab Friabilator (USP) EF-

2. Tablets were prepared by wet granulation using formula mentioned in (Table 1). Likewise, in a Modified DC trial, polyvinylpyrrolidone (PVP) K30 was used as binder immediately after oil loading. PVP K30 was dispersed in ethanol and added upon oil loaded MSG. Prepared blend was mixed thoroughly and allowed to dry at 50°C. Afterwards, the dried powder was mixed with other excipients excluding pregelatinised starch and compensated with MCC. Tablet hardness for all formulations was measured with an EH 01 tablet hardness tester (Electrolab, India) at tablet weight of 500±5mg. Various trials were conducted with above three methods to formulate the maximum amount of oil loaded MSG (10 to 70%, w/w) in tablet dosage form. The effect of the temperature on the blend flow property and tablet hardness was studied by keeping the blend at a constant temperature such as 10°C, 25°C and 40°C and measuring flow properties like AR, TD, BD, CI and HR as the blend was compressed into tablets. Tablets prepared with 40% of oil loaded carriers (MSG, GFS and MAS) at 20 KN compression force were subjected to dissolution studies. An aliquot of 2mL was withdrawn at predetermined time intervals and filtered through 0.22µm membrane filter. The dissolution samples were analyzed by using an HPLC method as described above.

Table 1: Formulation for tablets (oil loaded carrier)

Ingredients % w/w	DC	WG
Vit E loaded MSG (1:1)	40.0	60.0
MCC PH102	45.5	30.5
Pregelatinized Starch	10.0	0
PVP K-30	0	5.0
Ac-Di-Sol	3.0	3.0
Syloid® 244FP	1.0	1.0
Magnesium stearate	0.5	0.5
granulating liquid (Ethanol)	0	q.s

DC is direct compression, WG is wet granulation, MSG is mesoporous silica gel

The maximum fill volume of Vitamin E loaded carriers in '0' size capsules was determined. An equal amount of oil loaded carrier (1:1) was filled in capsules and subjected to dissolution study using USP apparatus I (DS 8000, Lab India, Mumbai). The dissolution media, 1% (w/v) SLS in water was used for both tablets (USP Apparatus II) and capsules at 75rpm, 37°C. An aliquot of 5mL was withdrawn after 45min and analyzed using HPLC method as described above.

2.7.2 Preparation and characterization of Glyburide solid SMEDDS

Formulations were prepared by dissolving a weighed amount of Glyburide in a mixture of surfactant, oil, co-surfactant and co-solvent at 25°C (Table 2). The final mixture was vortexed until a clear solution was obtained. The final content of drug in the formulation was 30mg/mL. This formulation was loaded on MSG in a ratio of 1:1 (solid SMEDDS) under continuous stirring. The successful preparation of a SMEDDS formulation was confirmed by the globule size determination using Zetasizer nano ZS, Version 2.2 (Malvern Instrument Ltd). Zeta potential (ZP) values were also determined using the same instrument. Samples were prepared by diluting the formulation with de-ionized water in 1:100 dilutions. Tablets of solid SMEDDS were compressed using tablet excipients and evaluated for physical properties like hardness, thickness, friability and disintegration time. The tablet which was equivalent to 5mg of Glyburide was used for *in vitro* dissolution studies. The study was carried out using 0.05M borate buffer (500mL, pH 9.5) as the dissolution medium in USP apparatus II (Lab India) at 37±1°C and at 75±1rpm. An aliquot of 5mL was withdrawn at predetermined time intervals and filtered through 0.45µm membrane filter. An equal volume of fresh dissolution medium was replaced. The dissolution samples were analyzed by using HPLC.

Table 2: Composition of SEDDS Preparation

Ingredients	Description	Composition, %w/w
Glyburide	API	3.0
N-Methyl-2-pyrrolidone	Co-solvent	10.0
Labrafac® Lipophile WL 1349	Oil Phase	10.0
Labrasol®	Co-surfactant	37.0
Cremophor® EL	Surfactant	40.0

Where SEDDS is Self emulsifying drug delivery system, API is active pharmaceutical ingredient

2.7.3 Compatibility of MSG and oil loaded MSG in capsules

MSG and Cremophor® EL loaded MSG (1:1) were filled in hard gelatin and hydroxypropyl methylcellulose, HPMC

(Vcaps® Plus) capsules by Capsugel. Filled capsules were stored in an upright position at RT for 2 weeks at defined relative humidity values (i.e. 2.5%, 10%, 30%, 50%, 65% and 70%). The weight variation of the capsules was determined and visual deformation or physical alteration of the capsules was monitored at defined time points. Furthermore, at the end of three weeks, the brittleness of the capsules was evaluated by dropping a standardized weight from a standardized height on filled closed capsules. The water content of the capsule shells stored under the same conditions was determined and correlated with the percentage of the broken capsules obtained. Disintegration time of the capsules stored at 40°C/75%RH for three weeks was determined using standard EP method.

3 Results and Discussion

3.1 Particle size and morphology

Particle size of carriers influences flow properties [23], compressibility [24], oil adsorption and desorption [25]. The particle size was measured using the Laser diffraction technology from Malvern®, Mastersizer® 2000. The two different sizes of MSG, 50µm (MSG 3050) and 150 µm (MSG 3150), represent narrow particle size distribution while both GFS and MAS were observed to have wide distribution. The oil adsorption and oil desorption processes are diffusion controlled [26, 27]. The pore channel length and volume varies according to the size of the particles [28], and hence, the time needed to fill the oil in the particle pores will be affected by the size of the particles. As a result the narrow particle size distribution supports a defined adsorption/desorption profile with more consistent kinetics compared to an adsorbent with wider particle size distribution (Figure 1) [29]. Surface area of MSG was found to be 320m^2/g by BET study, while reported area for GFS and MAS was 300m^2/g. SEM pictures were taken to learn more about shapes, sizes and surface of the studied adsorbents. As shown in Figure 2, MSG is irregularly shaped with aspect ratios from 1:1 to 2:1 and has a quite narrow particle size distribution with uneven surface. The GFS is spheroidal in shape with an aspect ratio of about 1:1 showing much broader particle size distribution than MSG. The surface appears to be comparatively smooth. MAS is spheroid with an aspect ratio close to 2:1. Its particle size distribution is broader than that of MSG (Figure 1). Its surface is smooth, but it is suggesting a kind of surface porosity.

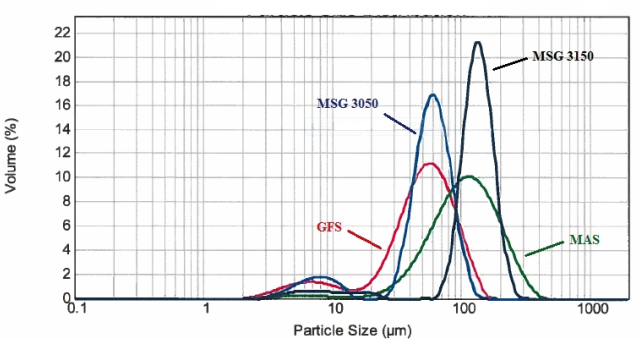

Figure 1: Particle size distribution of MAS (magnesium aluminium silicate), GFS (granulated fumed silica) and MSG (mesoporous silica gel) of two sizes.

3.2 Pore size Distribution by Hg intrusion-extrusion study

Hg is a non-wetting liquid for silica and must be forced to penetrate the pores. Generally, the penetration pressure is related to the pore radius of the particle (small pores requires high pressure). The volume of penetrated Hg can be seen as pore volume. The intrusion-extrusion curves of MSG and GFS (Figure 3) have shown ~2200mm^3/g of pore volume compared to ~4000mm^3/g with MAS. Mercury will also fill the intra pore volume (pores between particles) at lower pressure. Out of this data we can see a significant higher pore volume and pore size distribution of MAS compared to MSG and GFS (Figure 4). This indicates the higher adsorption capacity of MAS. This difference between intrusion-extrusion (hysteresis) is often caused by lack of pore uniformity, to the point of bottleneck pores. Although MAS showed higher adsorption capacity it exhibits relatively poor desorption (detailed discussion under oil desorption study). The model of the bottle-neck pores may explain the difference between high adsorption capacity and low desorption. The mercury hysteresis hereby confirm the observations by oil adsorption and desorption studies. Interestingly, MSG and GFS, which have significant differences in synthesis and morphology, have a very similar pore size distribution. (MSG: micron sized primary particles with intraporosity received through a pH, concentration and temperature dependent process – Ostwald ripening; GFS: micron sized granulate with intraporosity received out of traditional nanosized fumed silica with interporosity through a pyrogenic process).

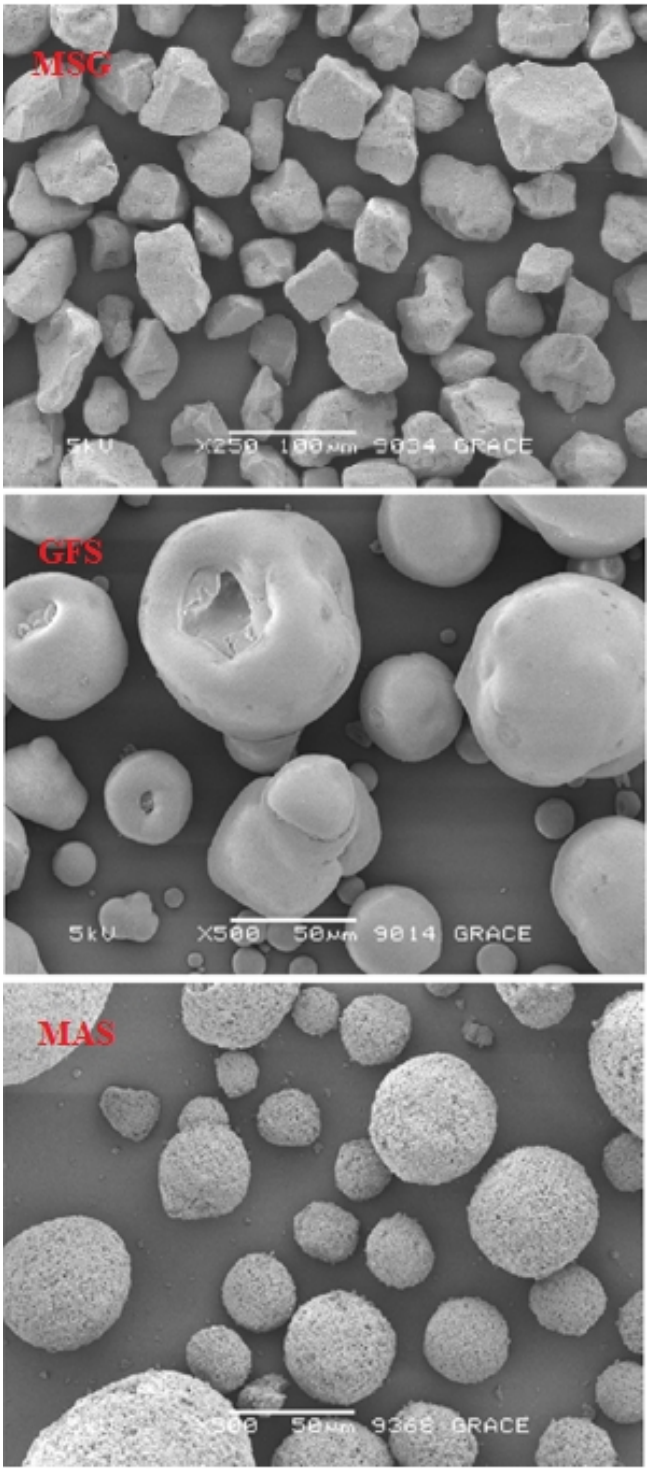

Figure 2: SEM images of MAS (magnesium aluminium silicate), GFS (granulated fumed silica) and MSG (mesoporous silica gel).

3.3 Flow properties for adsorbent carrier

Maintaining the proper powder flow is a concern for manufacturing pharmaceutical solid dosage forms. In addition, good flow is a challenge if API or formulation components

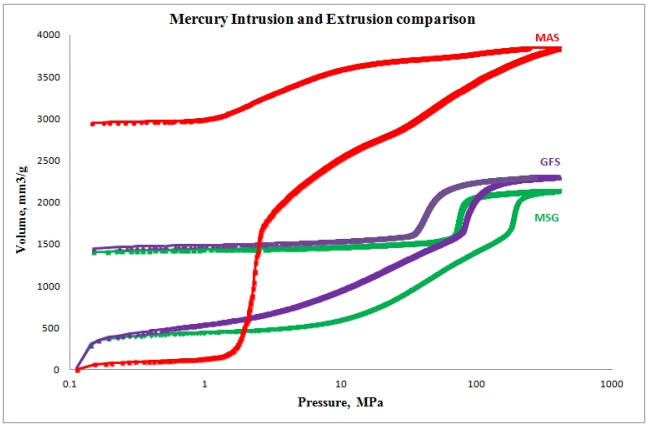

Figure 3: Intrusion extrusion study for MAS (magnesium aluminium silicate), GFS (granulated fumed silica) and MSG (mesoporous silica gel).

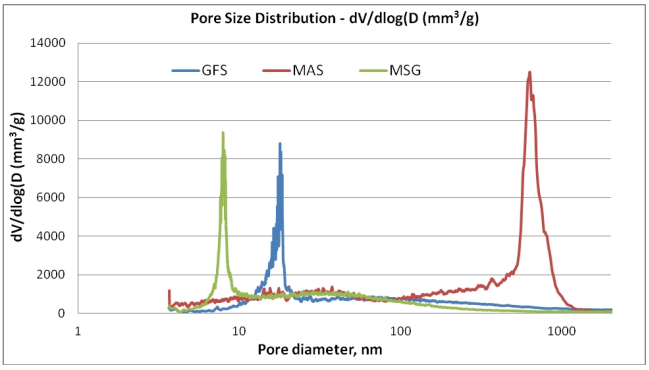

Figure 4: Pore distribution of MAS (magnesium aluminium silicate), GFS (granulated fumed silica) and MSG (mesoporous silica gel).

are oils or lipids. Therefore, adsorbent carriers designed for such formulations must possess desired flow property to avoid poor content uniformity, poor die fill and caking during die and capsule filling. The observations of flow properties for different adsorbent carriers are summarized in Table 3. From the results, it can be concluded that all the adsorbent carriers exhibit good (according to pharmacopeia terminology) flow behavior. BD of powder blend plays a major role in formulation development of tablet and capsules. In tablets manufacturing, low density results in poor flow, less compressibility and die filling while in capsules, only limited quantity can be delivered in defined capsule volume. Also, dusting can be an issue with low density products during manufacturing and filling. BD and TD of MSG are higher than both MAS and GFS, indicating that the MSG carrier is more suitable for capsule dosage form, where we expect higher loading per unit volume (volumetric adsorptive capacity). No significant difference in CI and HR was found for all carriers.

3.4 Maximum oil adsorption study

Adsorbent carriers are excellent choice for oils and lipids delivery. However, as discussed, an optimized adsorbent is one which carries maximum oil, maintains same flow properties as the native adsorbents, ensures maximum storage stability and releases maximum oil in the GIT fluid. Comparative observations of flow properties of 'loaded powders' and maximum oil adsorption are mentioned in Table 3 and Table 4, respectively. Oil adsorption capacities ranged from 285–373g/100g of MSG, 308–391g/100g of MAS, while for GFS it was 266–360g/100g. Oil adsorption capacity for non-silica based carriers ranged from 57–127g/100 g which are significantly lower compared to MSG (Figure 5). Although, oil adsorption capacity for MAS is higher, the increased CI limits its use beyond 1:1.5 ratios. On the contrary, MSG has a significantly lower CI to indicate good flow properties for die and capsule filling. Since oil adsorption of non-silica based carriers was significantly less than silica carriers, we decided to focus on silica based carriers for further study.

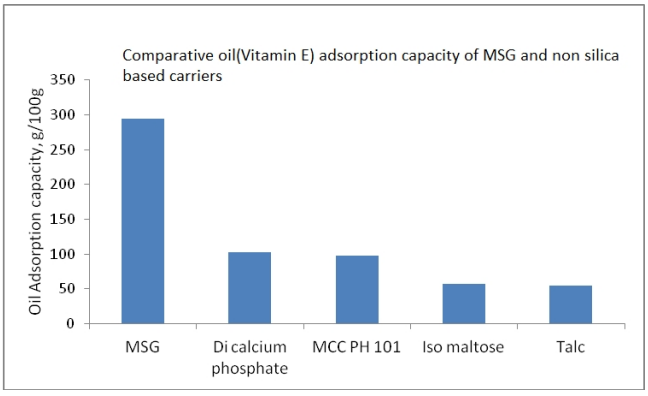

Figure 5: Maximum oil adsorption study for non-silica carriers *vs* MSG (mesoporous silica gel).

3.5 Flow properties for Vitamin E loaded carrier

Flow properties of Vitamin E loaded carriers remained the same with increased oil loading from 1:1 to 1:1.5, with the exception of MAS where AR increased from 35 to 37 (Table 3). Further increase in oil loading (1:2) generates sticky powder with poor flow rate. A 1:1.5 ratio can be considered as the threshold limit for oil loading. For MSG, flow properties remained consistent before and after oil loading which indicates complete adsorption of oil on MSG and virtually no oil remained on surface.

Table 3: Flow properties of Vitamin E loaded carriers

Carrier: Oil ratio	Flow properties for Vitamin E loaded carriers				
	AR, °	**BD, g/mL**	**TD, g/mL**	**CI, %**	**HR**
MSG (1:0)	31.27	0.25	0.29	13.79	1.16
MSG (1:0.25)	31.89	0.28	0.35	20.00	1.25
MSG (1:0.5)	32.91	0.34	0.42	19.04	1.23
MSG (1:1)	33.29	0.46	0.54	14.81	1.17
MSG (1:1.5)	34.20	0.57	0.71	19.71	1.24
MAS (1:0)	30.60	0.17	0.20	15.00	1.18
MAS (1:0.25)	35.85	0.19	0.23	17.39	1.21
MAS (1:0.5)	35.11	0.22	0.28	21.42	1.27
MAS (1:1)	35.82	0.26	0.33	21.21	1.27
MAS (1:1.5)	37.28	0.33	0.41	19.51	1.24
GFS (1:0)	27.81	0.21	0.27	22.22	1.28
GFS (1:0.25)	29.84	0.27	0.33	18.18	1.22
GFS (1:0.5)	29.92	0.33	0.39	15.38	1.18
GFS (1:1)	33.64	0.46	0.56	17.85	1.22
GFS (1:1.5)	34.29	0.50	0.61	18.03	1.22

Where, MSG is mesoporous silica gel, GFS is granulated fumed silica, MAS is magnesium aluminum silicate, ND=Not determined because of lump formation; Oil loaded blend physical properties such as AR is angle of repose, BD is bulk density, TD is tapped density, CI is compressibility index, and HR is Hausner ratio were evaluated prior to formulation development.

3.6 Effect of humidity on oil adsorption

Samples of carrier kept at high humidity conditions (90% RH and 24°C, 4 days) were studied for oil adsorption and the observations are shown in Table 5. To correlate the effect of humidity with oil adsorption, LOD was measured on the 4th day and compared with maximum oil adsorption. The observations indicate, MAS is more affected by humidity than MSG and GFS. MAS has adsorbed nearly 7 times its initial moisture on day 4, while MSG and GFS had adsorbed only twice the intial moisture. High humidity can significantly decrease, the oil adsorption capacity for carriers like MAS, but for MSG and GFS, capacity remains nearly the same. This can be attributed to moisture occupied pores limiting oil adsorption of MAS. Obser-

Table 4: Maximum Oil absorption capacity for silica carriers (at RT, 60% RH)

Oil used	MSG, g of oil /100 g	MAS, g of oil /100 g	GFS, g of oil /100 g
Captex 355*	297.01 ± 3.61	345.67 ± 7.09	281.00 ± 4.51
Labrafac PG*	285.00 ± 3.46	384.65 ± 7.01	272.91 ± 9.45
Capmul MCM*	274.33 ± 10.50	393.02 ± 5.06	275.03 ± 7.21
Labrasol*	322.33 ± 2.89	411.12 ± 8.19	303.31 ± 5.69
Labrafil M 1944 CS*	287.67 ± 4.51	391.67 ± 4.04	264.00 ± 4.97
Transcutol HP	306	340	276
Solutol HS 15	312	322	306
Cremophor EL	317	363	328
Transcutol HP	306	340	276
Capryol 90	296	335	268
Linseed oil	294	330	295
Eucalyptus oil	291	324	288
Lemon grass oil	296	322	295
Peppermint oil	285	320	271
Castor oil	326	345	273
Sesame oil	299	336	277
Olive oil	290	345	266
Clove oil	373	391	360
Oleic acid	290	335	269

* n=3 for selected oils and for remaining oils n=1. MSG is mesoporous silica gel, GFS is granulated fumed silica, MAS is magnesium aluminum silicate

vations of Kutza *et al.* suggest that adsorbents with high moisture content have less oil adhesion and must be stored at constant temperature and humidity conditions [31].

3.7 Oil desorption study

In order to achieve desired bioavailability, drugs must be desorbed from the carrier/dosage form in sufficient time to be dissolved and absorbed through the GIT. Accordingly, carriers must desorb 100% or close to 100% oil/lipid in GIT fluid to initiate drug dissolution and absorption process. To allow this, the adsorbent should not have a strong binding with oil/lipid. Various adsorbents were evaluated for efficient oil desorption and release, to define possible bioavailability problems. Desorption study signifies the recovery of adsorbed oil while release study was conducted to understand the kinetics of oil release from carriers. The desorption study was conducted using water as the desorption media and centrifugation at 5000 rpm, 10 min at 23°C, 60%RH. The obtained observations suggest that MSG and GFS desorb oil efficiently (85%) while relatively poor desorption was observed with MAS (38%), which is ascribed to the earlier described wide pore size distribution providing bottleneck problems. As shown in Figure 6, a milky emulsion is formed for MAS in the centrifuge tube while we could see clear desorption of oil from GFS and MSG. Similarly, various authors have reported poor drug and/or oil release from a carrier like MAS [30]. The obtained observations are comparable with Kang *et al.* who reported slow and incomplete ibuprofen release from SMEDD formulation loaded with MAS [32]. In addition, Van Speybroeck *et al.* observed incomplete desorption of danazol through MAS loaded SMEDD formulation [11]. Various researchers had attempted to determine the reason behind the poor release through adsorbent formulations. According to Zhang *et al.*, oil desorption from the adsorbent carrier is affected by pore diameter [31, 33], pore channel length [32, 33, 35], and chemical moieties on the pore surface [34, 36]. Furthermore, Kutza *et al.* found that stronger hydrogen bonding of oil with adsorbent decreases oil release [31]. Smaller pore diameter, larger pore channel lengths and stronger hydrogen bonding could be factors associated with slow and incomplete oil release from MAS [35, 37]. As described earlier, pore size distribution and its related bottleneck problems an additional parameter will be considered.

3.8 Effect of surfactant and surface silanols on oil desorption

Tween 80 (3%) was used as a surfactant along with water in desorption media to increase the surface wettability of the carrier. It was observed that the presence of a surfactant helps coax out slightly more oil from MSG and GFS carriers (86% and 84%, repectively) when compared to the observations of desorption without surfactant (76% and 74%, respectively). In the case of MAS, the effect of surfactant was reversed. Increased surfactant concentration in desorption media has decreased % oil desorption significantly from MAS. The observed desorption for MAS containing desorption media without and with surfactant were 42% and 36%, respectively. This could be due to interaction of Tween 80 with MAS. Further understanding of the molecular determinants of the interaction with MAS was beyond the scope of the current study, but is the subject of ongoing investigations. Furthermore, it is reported

Table 5: Effect of humidity on oil adsorption

Carrier	LOD, %		Max oil adsorption, g/100g		% Decrease
	0 day at 60%	4th day at 90% RH	0 day at 60%	4th day at 90% RH	
MAS	3.34	21.93	363	336	7.43
GFS	4.72	10.58	328	309	5.79
MSG	3.78	9.68	323	315	2.47

Loss on drying (LOD) and Max oil adsorption values for different silica carriers.

that Cremophor EL has affinity to MAS causing a reduction in danazol release from the solid SMEDDS [11]. To better understand the role of silanol/hydroxyl groups in the interaction with the liquids calcination was performed to reduce the possibility of H-bonding. Interestingly, there was no oil desorption after calcinations. In addition, the surfactant did not help in the improvement of the oil release from MSG with reduced silanol content by calcinations. This confirms the importance of silanol groups and their role in effective oil desorption [36, 38].

3.9 Development of solid oil/lipid and solid SEDDS using MSG as adsorbent

3.9.1 Preparation of tablet and capsule as dosage form for oil and lipid delivery

Because MSG seems to be an effective carrier for oils and lipids as a result of its maximum oil loading, flow properties, BD, stability at higher humidity, SEDDS and oil desorption, it is important to understand its suitability in solid dosage forms like tablet and capsules. Various formulations were evaluated with in-process quality control parameters like hardness, friability, tablet thickness and disintegration time. Among all formulation approaches attempted, the direct compression (DC) method was the most simple and effective. A maximum of 40% of oil loaded carrier can be formulated in a tablet using conventional DC method and 60% of the oil loaded carrier can be formulated by wet granulation. The amount can be increased up to 70% by using a dispersion of PVP in ethanol as a binder (modified DC method) just after oil loading. The observations from three trials are presented in Table 6. Utilizing various formulation skills, it is possible to load 70% oil-loaded MSG carrier in a tablet without significantly compromising the physical properties of the dosage form. Tablet hardness at higher loading can be improved by reducing the punch size.

Table 6: Observations of tablet trials

Parameter	DC	WG	Modified DC
% Oil loaded carrier (MSG)	40%	60%	70%
Target tablet weight, mg	500 mg	500 mg	500 mg
Hardness, N	60 N	50 N	45 N
Disintegration time, min	1	2	3
Friability, %	<1	<1	<1
Compression force, KN	20	20	20
Turret speed, RPM	5	5	5
Ejection force, N	90-100	90	80

MSG is mesoporous silica gel, GFS is granulated fumed silica, and MAS is magnesium aluminum silicate

3.9.2 Effect of temperature on blend flow properties and tablet hardness

Adsorbed oil may get solidified at low temperature while at high temperature the viscosity of the oil will be decreased and it may come onto the surface of tablet. To confirm, the Vitamin E loaded MSG was compressed at various temperatures and the compression forces used to determine the threshold limit. At compression forces of 10, 15 and 20KN tablets displayed hardness of 35, 55 and 40N respectively. The highest hardness was observed at 15KN compression force and there was no effect of the temperature (10°C, 25°C and 40°C) on tablet hardness at all compression forces tested. Also, no significant effect of the temperature was observed on flow properties, indicating that the oil/lipid remains intact in MSG pores at wide range of temperatures and oil-loaded MSG concentrations, demonstrating the suitability of MSG as a carrier under most normal operating conditions.

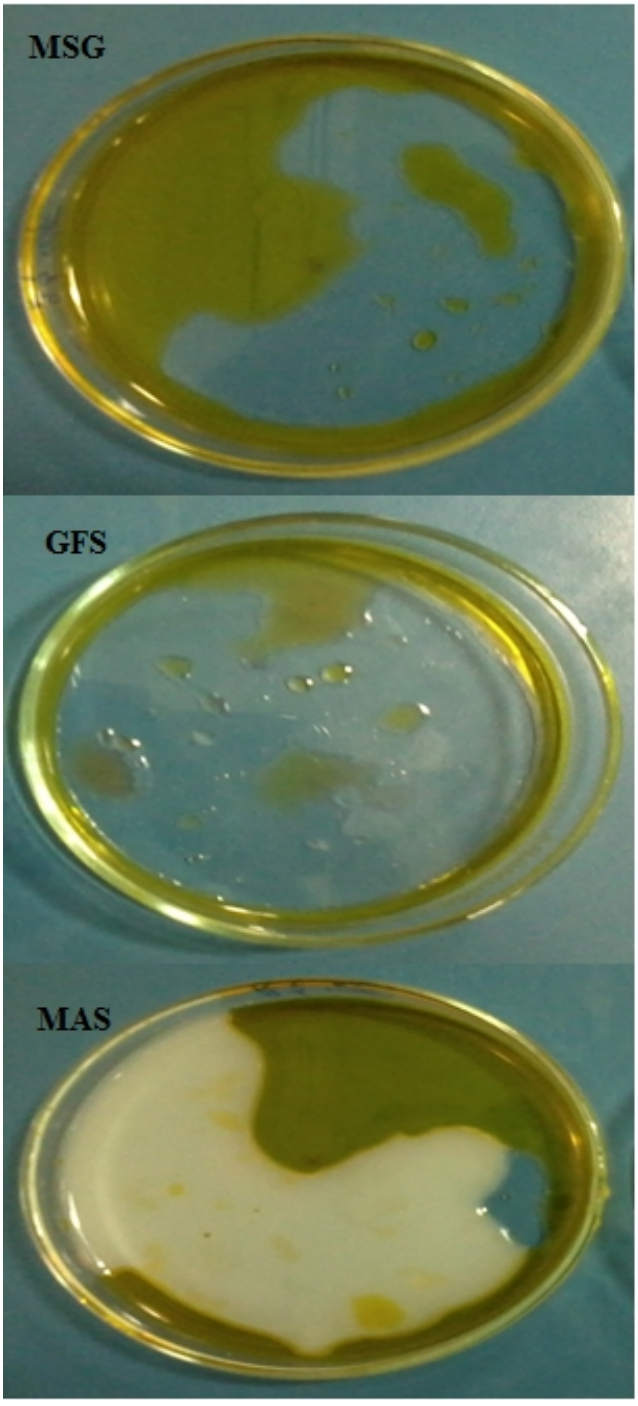

Figure 6: Images of Vitamin E desorption from MAS (magnesium aluminium silicate), GFS (granulated fumed silica) and MSG (mesoporous silica gel).

3.9.3 Oily drug (Vitamin E) release from tablets and capsules

Tablets prepared with MSG exhibited the most complete release of oil within 45min, followed by GFS and MAS. Capsules filled with oil-loaded adsorbents were subjected to dissolution testing and the observed results are presented in Figure 9. Vitamin E release from capsules filled with three carriers was also conducted (Figure 9). Additionally, dissolution studies were conducted for 1:1 Vitamin E loaded carrier only to understand any interaction between the carrier and capsule shell. Observations indicate there were no interactions.

3.9.4 Preparation and characterization of Glyburide solid SEDDS

Silicates can be utilized for the development of oral solid SMEDDS, especially to enhance dissolution rate and bioavailability of poorly water-soluble drugs by adsorbing them in an amorphous form [37, 39]. A liquid SEDDS preparation was found to be a clear solution and solid SMEDDS was found to be a free flowing powder after adsorbing on carriers. Optimized solid SMEDDS is one which generates similar globule size in GIT as of liquid SMEDDS so that intended drug absorption is not affected due to adsorbent. Hence, both liquid and solid SMEDDS were characterized by globule size determination in water. Observations of globule size analysis of placebo liquid SMEDDS, drug loaded liquid SMEDDS and solid SMEDDS are presented in Figure 7. Furthermore, ZP values were ranged between −22 to −25 mV. This indicates that the surface charge of globules is unaffected by the MSG as adsorbent carrier. This surface charge helps to stabilize dispersion in colloidal state [38, 40]. The globule size of both the placebo and liquid SMEDDS was found to be same (19 nm), which indicates optimized formulation of SMEDDS. The extra peak of size (170 nm) in solid SMEDDS may be attributed to the adsorption of lipids or surfactants on the surface of MSG. If the adsorbents possess more affinity towards lipids or surfactants, the content of the surfactant in the dissolution media will be reduced and the emulsification will be poor with increased globule size [11]. However, a prominent peak is observed at 19nm size corresponding to the globules of SMEDDS and the observed dissolution capacity (Figure 8).

The solid SMEDDS preparation showed > 90% release at 45 min (Figure 8) due to the effect of the surfactants and co-surfactants involved in the formulations resulting in decreased agglomeration and increased wettability in aqueous media. On the other hand, only a 65% release was observed with Glyburide alone.

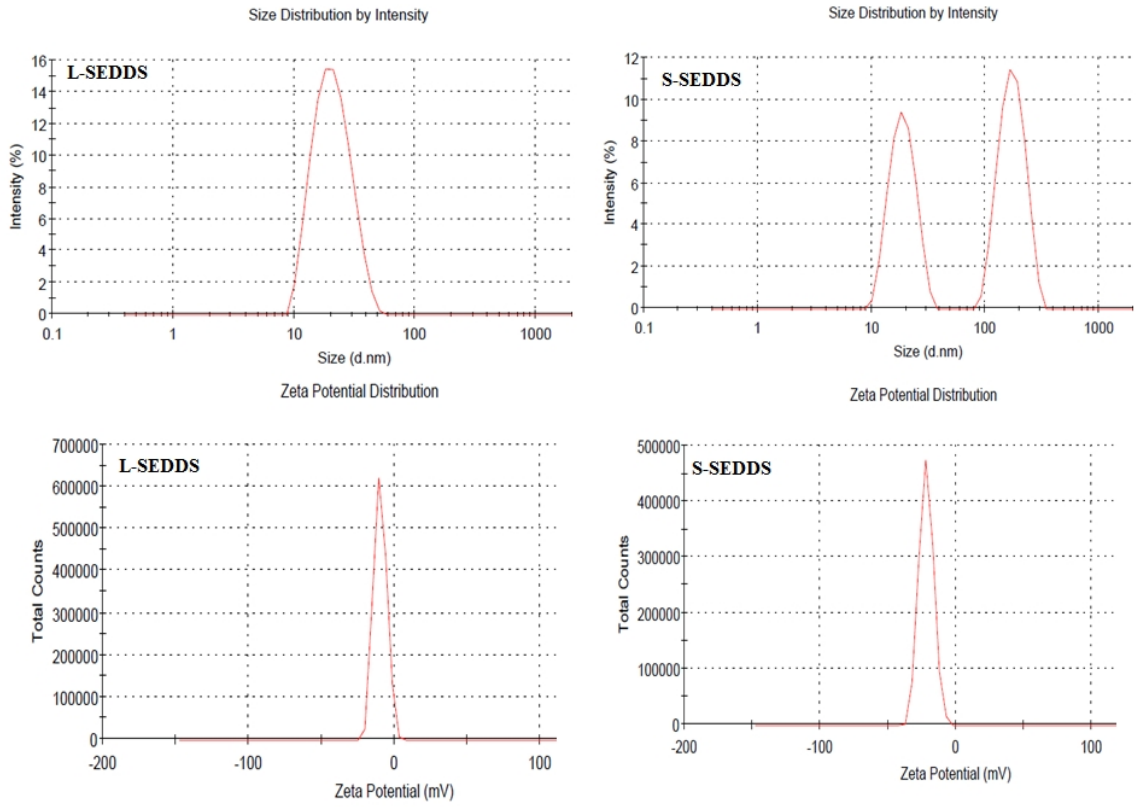

Figure 7: Globule size and Zeta potential of liquid SMEDDS and solid SMEDDS of Glyburide.

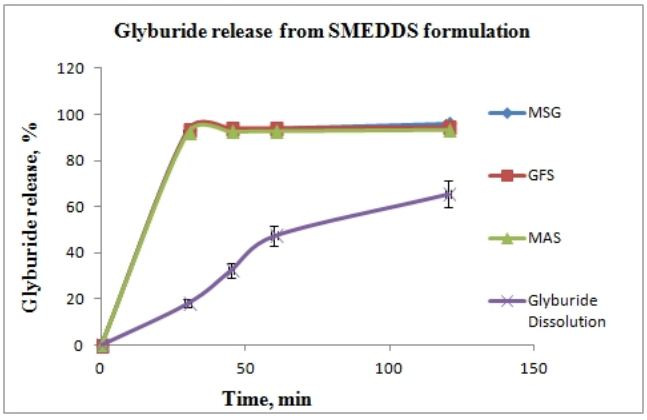

Figure 8: Glyburide release from surfactant containing solid-SMEDDS formulation.

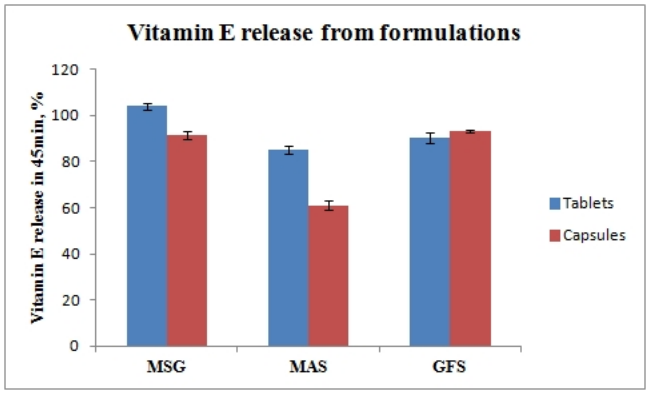

Figure 9: Vitamin E release from tablets and capsules prepared with Vitamin E adsrobed on MAS (magnesium aluminium silicate), GFS (granulated fumed silica).

3.9.5 Compatibility of oil loaded MSG in capsules

Hygroscopic materials such as silica may cause brittleness of gelatin capsule shells. Hence, the capsule compatibility program was initiated with both gelatin and HPMC capsules (Vcaps® Plus) as per Capsugel's standard procedures. The obtained observations claim neither deformation nor any alternation in either the gelatin or the HPMC capsule shells during the execution of the compatibility program. Neither MSG nor Cremophor® loaded MSG generated brittleness issues under the tested humidity conditions (Table 7). This may be attributed to the low capillary forces of the large pore size MSG resulting in reduced hygroscopicity. The observations of the disintegration study (Table 7) were in compliance with the EP monograph 2.9.1 with a total disintegration time below

Table 7: Disintegration of MSG and Cremophor® EL loaded MSG capsules (after 3 weeks, at 40°C, 75%RH)

MSG	Gelatin capsules	Opening time, min	<2
		Total disintegration time, min	<11
	Vcaps® Plus HPMC capsules	Opening time, min	<3
		Total disintegration time, min	<9
Cremophor® EL loaded MSG	Gelatin capsules	Opening time, min	<3
		Total disintegration time, min	<11
	Vcaps® Plus HPMC capsules	Opening time, min	<2
		Total disintegration time, min	<11
MSG is mesoporous silica gel			

30 min. This indicated that no major interactions took place between the fills and capsule shells as may happen if certain cross-linking ingredients are present in the fill [41, 42]. Hence, it can be concluded that both MSG and Cremophor® EL loaded MSG are compatible with gelatin and Vcaps® Plus capsules under all standard storage conditions of 15 to 25°C and 35–65% RH.

4 Conclusion

All three solid porous carriers studied are found to have adequate flow properties. As opposed to the other carriers, the flow properties of MSG and oil loaded MSG do not change significantly, and MSG has a higher bulk density allowing for easy processing and the ability to deliver maximum amounts of liquid in a given volume such as a capsule (volumetric adsorptive capacity). All carriers found to be acceptable (average 1 carrier:3 oil) in the oil adsorption study (Table 4); oil desorption however was observed to differ between carriers with oil desorption of MSG=GFS>MAS. According to the Glyburide release study, MSG is able to carry SMEDDS formulations adequately and more effectively. Oil loaded MSG can be formulated in both tablets and capsules. In conventional DC tablets, a maximum of 40% can be delivered while up to 70% can be formulated using PVP ethanol dispersion as a binder. In terms of oil release from a tablet, MSG=GFS>MAS. In capsules, the highest amount of oil loaded MSG can be delivered as compared to MAS and GFS and also MSG demonstrated maximum oil release compared to GFS and MAS. Also, both MSG and oil loaded MSG is proven to be compatible with gelatin and Vcaps® HPMC capsules. It can be concluded that highly porous silicate carriers are an adequate choice for pharmaceutical formulators in delivery of oil and lipid based formulations. Ongoing investigations are required to understand the molecular interactions that may occur with the adsorbent and to understand how GIT enzymes may play a role in driving desorption.

Declaration of interest:
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