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"COMPARATIVE STUDY OF THREE GRANULATION TECHNIQUES: MOISTURE ASSISTED GRANULATION TECHNIQUE, ROLLER COMPACTION AND HOT MELT EXTRUSION TECHNIQUE WITH MALTODEXTRIN DE16, PVP K 12 AND HPC AS POLYMERIC BINDERS"

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ABSTRACT

Three granulation processing methods; Hot melt extrusion (HME), Roller compaction Dry granulation (RCDG) and Moisture assisted dry granulation (MADG) are assessed to evaluate different polymeric binders for preparation of a high dose immediate release tablet of acetaminophen drug. Different characterization techniques were used to enumerate poor physical property characteristic for drug (paracetamol) including hygroscopicity, low solubility and bulk density, and poor powder flowability. In case of maltodextrin all techniques produce uniform granules while, HPC produce more fine particles. A massive enhancement in drug loading of 8.5:1.5 was achieved via hot melt extrusion process using low molecular weight polymeric-binders as PVP K12, HPC SSL and Maltodextrin. Granules produced by melt processing contained less fines as compared to MADG and RCDG. A formulation and process for dry granulation by roller compaction was also developed. Particle size distributions of milled ribbons were analysed by sieve analysis. Higher density granules produced with roll force of 15 kN/cm and improved flow properties and less fines content (<75 μm) was observed. Drug loading (API:excipient ratio) in roller compaction was 8:2. IR formulation of acetaminophen was developed using MADG process and characterised for granular and tableting properties. Acceptable content uniformity, dissolution results were obtained using MADG and HME. While RCDG gives poor content uniformity tesults. Differential Scanning Calorimetry analysis suggested the amorphisation of the drug in the HME granules containing the three excipients. This result was then confirmed by X-ray powder diffraction analysis, hence higher dissolution rate for HME granules than RC and MADG granules. Both HME and MADG are viable granulation process choices for scale up to overcome the physical property limitations of Acetaminophen drug.

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INTRODUCTION

Desired results for content uniformity can be obtained by selection of proper granulation process. Different granulation processes are well established for tablet manufacturing process. Different types of granulation methods are available as per literature survey[1, 2]. Dry and wet granulation are most commonly used techniques. Dry granulation involves processes like slugging or chilsonation. In the literature survey, cross comparison of different dry and continuous granulation technologies using the same formulation is not widely discussed. One example found in the literature was comparison of a low-shear granulation vs. high-shear using common excipients. In this study the excipient levels, the mixer type and compression pressure were varied in the design of experiments[3]. A comparison, using a sematilide hydrochloride formulation, of moisture-activated dry granulation in a planetary mixer was performed vs. traditional wet granulation in a planetary mixer, roller compaction, and direct compression[4].The moist granulation technique was also compared to direct compression and wet granulation using an acetaminophen formulation[5]. The effect of manufacturing process using direct compression, wet granulation, extrusion-spheronization, dry granulation, and spray-drying on the initial dissolution of theophylline was also investigated[6]. For a high dose, poorly water soluble, low density micronized drug a comparison of fluid bed and high shear granulation was performed by Gao et al[7]. Granulation comparison studies help to choose the best method from many available technologies, so that the process engineer can develop the most robust process for the target formulation. The purpose of this study was to evaluate the use of different binders i.e. maltodextrin DE16, PVP K 12 and HPC SSL, in the production of improved dissolution acetominophen granules, using three granulation techniques namely moisture-activated dry granulation (MADG), roller compaction dry granulation (RCDG) and hot melt extrusion (HME) technology. The moisture-activated dry granulation (MADG) was developed by Ullah et al[8]. MADG is a simple and innovative process where granules are created with water and a granulating binder, as in wet granulation, but are not heat dried or milled. The endpoint sensitivity is minimised by this method. This process is also called as “one-pot process” because the whole process can be performed within a conventional high shear granulator. MADG has very few variables, resulting in lesser need for expensive PAT technology. Although, RCDG has been used in the pharmaceutical industry since more than 50 years, it has recently drawn increasing attention[9]. Roll compaction has many advantages over slugging namely greater production capacity, more control over operating parameters and dwell time minimal need for powder lubricant[10, 11]. More recently, hot melt granulation with excipients having low melting points is another technology to prepare granules. Unlike wet granulation, melt granulation does not require any binder solution or liquid. Instead, the drug substance is subjected to temperatures below its melting temperature but above the melting or glass transition temperature of the selected binders. Melt granulation processes has many advantages over conventional pharmaceutical granulation techniques namely, elimination of a drying phase, absence of solvents, fewer processing steps, and ability to process at high drug loading relative to excipients[12, 13]. Fluidized bed granulators[14-16], twin screw extruders[17] and high shear mixers[18] can be used in the process of Melt granulation.

Selected model drug Acetaminophen is an analgesic, shows poor water solubility, elastic deformation and has very poor compressibility. Also it gives too many fines or too many coarse particle with wet granulation due to poor solubility and compressibility[19].

The aim of this study was to compare three granulation techniques: Moisture assisted granulation technique, roller compaction and hot melt extrusion technique with maltodextrin DE16, PVP K 12 and HPC as polymeric binders using paracetamol as model drug.

MATERIALS

Acetaminophen (APAP) USP were obtained from Bajaj Healthcare Pvt Ltd., Mumbai, India, Plasdone® K 12 (Polyvinylpyrrolidone,PVP USP) was gifted by ISP, Wayne, NJ and Aeroperl® 300 pharma was provided as gift sample by Evonik Degussa India Pvt Ltd, Mumbai, India. MaltodextrinDE16 (SUNMALT®) was purchased from Gujarat Export Limited, India; Hydroxypropylcellulose (HPC-SSL®) was procured from NIPPON SODA, Mumbai, India; Magnesium stearate was purchased from Nitika Pharmaceutical Specialties Pvt. Ltd., INDIA.

METHODS

Solid state characterization of API

Physical characterization like Flow properties, SEM, DSC of acetaminophen drug was carried out.

Preparation of Granules

By MADG Method

A batch size of 240 gm was considered for formulation trials as shown in table 3. Drugs were sifted through 16 mesh screen and blended with the low viscosity grade binder Povidone K12, Maltodextrin DE16 and Nisso HPC SSL and granulated by spraying 2% w/w water for 15 s in the granulation bowl at 700 rpm impeller speed for 5 minutes. Followed by Aeroperl ®300 was added as a moisture absorbent at same speed (700 rpm impelled speed) for next 2 minutes. Pre-sieved lubricant magnesium stearate was added to the above blend in the granulator and blending was continued for 0.5 min at 300 rpm[20, 21].

By RCDG Method

A roller compactor (Clit Mini Roller Compactor, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India) was used for the development of a dry granulation for Acetaminophen. A hopper with a 2.5 L volume having bore diameter of 19 mm was used for charging the powder. Corrugated rolls of 100 mm in diameter and 25 mm in width were used for roller compaction. The process parameters established from the feasibility studies were a roll gap of 2 mm, feeder speed was 25 rpm and a roll speed of 6 rpm. Roll force was 15 kN/cm. These experiments were conducted at 500 gm scale. The highest drug to excipient ratio which could be successfully processed by roller compaction was 8:2. The resulting ribbons were milled to granules and were tested for particle size distribution and density (bulk and tapped).

By HME Method

Solid extrudes were prepared by hot melt extrusion using a single-screw extruder (made by S.B. Panchal ltd. Mumbai India). Acetaminophen was mixed with Maltodextrin, PVP K 12 and HPC SSL at drug/polymer mass ratios using a mortar-pestle for 5 min. The prepared physical mixtures (PMs) were extruded using a corotating single-screw extruder at a screw speed of 50 rpm. Die used for extrusion was of 10 mm diameter..Optimized batches were then processed using twin screw extruder instrument (ACG hot melt extruder) for the development of extrudate solid dosage formulation. The melt extrudate were milled using grinder, passed through a 200 µm sieve then kept inside glass vials with stopper in desiccator for storage stability studies. A suitable quantity of the physical mixture and extrudes from each was used for analysis. HME processing speed, extrusion temperature (Tgmix) and Feeding rate were found to be controllable parameters in the process that could affect chemical stability of formulation. All extrusions were performed in triplicate to measure the processing torque and mean residence time. Summary of Extrusion parameters used for drug and polymer that are shown in Table 1.

Measurements of Physical Properties of Granules

Particle size distribution

Sieve analysis was performed using 25 g of granules and a series of U.S. standard sieves of mesh size corresponding to 850µm, 600µm, 300µm, 250µm, 180µm, 150µm, 75µm. The granules were placed on the top sieve and mechanically shaken for 10 min using Electromagnetic sieve shaker (Electrolab Pvt Ltd.). The weight of fraction retained on each screen was taken and particle size distribution was obtained.

Scanning Electron Microscope

Scanning electron microscopy (SEM) was performed to observe granule growth and shape development as a function of polymeric binder. Microscope imagines of granules were taken using XL 30 Model, JEOL 5400, Japan.

DSC Analysis

DSC analysis of Lubricant samples were carried on Perkin Elmer pyris-6 (USA) which has in built a computerized data station for thermal analysis. Samples (about 4 mg) were heated in the aluminum pan in 40-300°C temperature range (at a rate of 10°C/min) under nitrogen flow (20 ml/min) using reference as an empty sealed pan. The obtained spectra were then studied for thermal transition like glass transition temperature and change in heat capacity.

Powder X-ray Diffraction

Crystallinity in raw materials, hot-melt extrudates and physical mixtures was determined using A MiniFlex II desktop powder X-ray diffractometer (Rigaku Corporation, Japan) equipped with Ni-filtered, Cu Kβ radiation, at a voltage of 30 kV and a current of 15 mA. The samples were pulverised in a ball mill chamber with a frequency of 25 s−1 for 30 s. The powdered sample was placed on a glass top loading holder with a depression of 0.2 mm and then gently consolidated. All samples were scanned in continuous mode within the angular range 3– 40° 2θ with a scan speed of 2.0° min−1 and sample width of 0.03°.

Granule strength

The granule strengths of all compound granulated with various binders were measured. To evaluate the breakage behaviour of granules, a repeated impact test was used. In this test, about 200 granules of each sample were fed into 100 particle-wall impacts per second with controlled impact velocity. The fracture fraction was calculated using the following formula [22, 23].

Fracture fraction = (sample weight − weight retained) / sample weight

Preparation and Evaluation of Tablets

Granules were compressed to obtain tablets. Tablets were evaluated for parameters affecting tabletting behaviour. Tablets were punched using Cadmach® rotary tablet press machine equipped with 9/18 inch diameter, standard concave punch to a final tablet weight of 600 mg. Tablets were compressed at different compression forces 2.5 kN,5.0 kN, 7.5 kN, 10.0 kN and 15.0 kN and *25* rpm**.** Weight variation, content uniformity, disintegration time, friability, thickness and hardness of the tablets was determined of 10 representative samples for each formulation.

***In vitro* drug dissolution study for IR tablet formulation**

Drug release from formulated and commercially available tablets of respective drugs, were performed using USP <711> Dissolution apparatus II at 50 rpm, 900 ml of phosphate buffer (pH 5.8) and 37°C ± 0.5°C by dissolution tester (Electrolab Pvt Ltd.). Withdrawn sample quantity was 5 ml at sampling time point. The average of the results was considered.

Stability studies

Accelerated stability studies was conducted for all the formulations as per the ICH guidelines (40 ± 2 °C and 75 ± 5% RH) for the period of 6 months in a stability chamber (Thermolab, Mumbai, India). In this study the samples were placed in vials with bromobutyl rubber plugs sealed with aluminum caps. Aliquots were withdrawn at 30, 60, 90 and 180 days and evaluated for the drug content and *in vitro* drug release.

RESULT AND DISCUSSION

Solid state characterization of API

The Acetaminophen is a weak base (pKa: 9.38), white crystalline powder. The molecular weight is 151.6 g/mol. The API melting peak temperature is 171°C by DSC, at a 10°C/min scan rate. Solubility is 4.2 mg/mL at 25°C. Acetaminophen is categorized as a BCS Class III. The API crystals are rod shaped, which contributes to very poor flow properties of the bulk API. The Carr's Index (compressibility) was 46%, indicating that Compound is categorized as having cohesive to very cohesive non-flowing characteristics (fig.1).

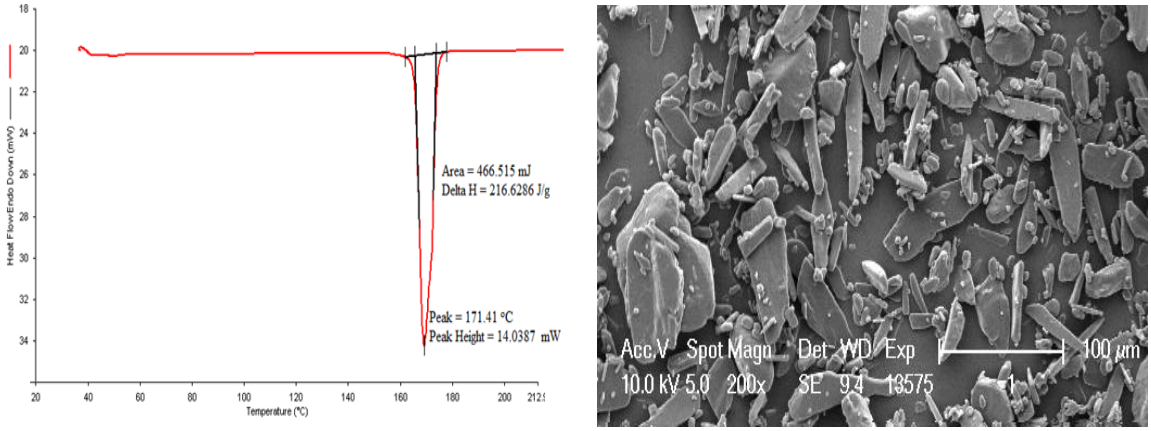


Fig. 1 Solid state characterization of acetaminophen.

Formulation composition

Table 1 Formulation composition by different granulation techniques.

Ingredients	Formulations								
	A	B	C	D	E	F	G	H	I
Active	83.33	83.33	83.33	84.5	84.5	84.5	80.50	80.50	80.50
Maltodextrin	12.67	-	-	15	-	-	19	-	-
PVP K 12	-	12.67	-	-	15	-	-	19	-
HPC	-	-	12.67	-	-	15	-	-	19
Aeroperl 300 Pharma	1.5	1.5	1.5	-	-	-	-	-	-
Water	2	2	2	-	-	-	-	-	-
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100	100	100

Methods – A,B,C-MADG Method; D,E,F – HME method; G,H,I –Roller compaction method.

Micromeritics Properties of granules

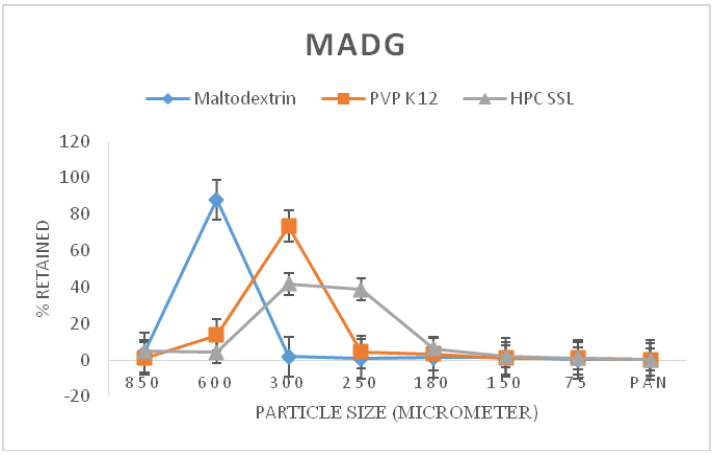
To evaluate the effect maltodextrin DE 16, PVP K 12 and HPC SSL polymeric binders in the granulation procedures, analysis and comparison of the characteristics of the final granules was carried out and found to be within USP limit (table 2). The results show that these excipients have different behaviour during the granulation process of these three methods. Maltodextrin DE 16 shows the best results among all formulations. This can be explained based on small particle size hence greater surface area and low viscosity of maltodextrin binder. Out of three granulation techniques roll compaction gave poor results while MADG gave best results.

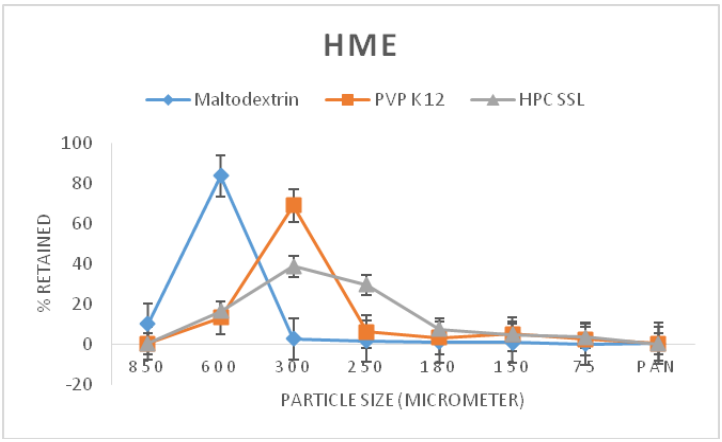
Table 2 Flow properties of granules.

Method	Binder	Bulk density	Tap density	Carr's index	Hausenr's ratio	Moisture content (%)	Angle of Repose (º)
MADG	Maltodextrin	0.62	0.67	7.50	1.08	2.23	22.90
	PVP K 12	0.56	0.62	13.60	1.17	2.21	23.00
	HPC	1.00	0.70	20.63	1.26	2.80	26.50
HME	Maltodextrin	0.50	0.58	15.00	1.17	1.21	26.20
	PVP K 12	0.47	0.58	19.04	1.23	1.11	27.33
	HPC	0.47	0.62	23.80	1.31	1.08	28.54
RCDG	Maltodextrin	0.47	0.62	23.80	1.31	2.99	30.6
	PVP K 12	0.43	0.58	19.04	1.35	2.43	33.2
	HPC	0.35	0.50	23.80	1.41	2.87	36.4

Particle size distribution

Fig. 2 shows the size distribution of the granules, in which the particle size of granules was in ranges from 650-250 µm; the use of Maltodextrin provided uniform granule size (x > 650 um) than others. Micromechanical properties of interparticle bridges formed by different polymeric binder differ on their viscosity. RCDG gave poor results as very fine and inconsistent particle size with PVP K 12 and HPC SSL. This may cause of elastic deformation of acetaminophen which produced poor compact even after two roll compaction. This is illustrated by plot in fig. 2.





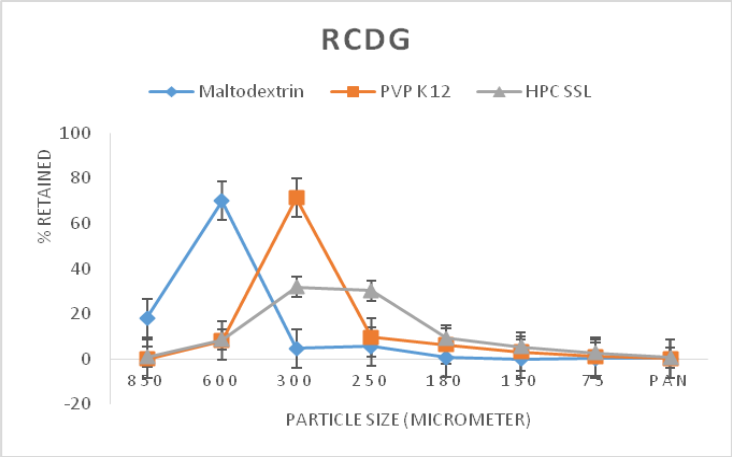
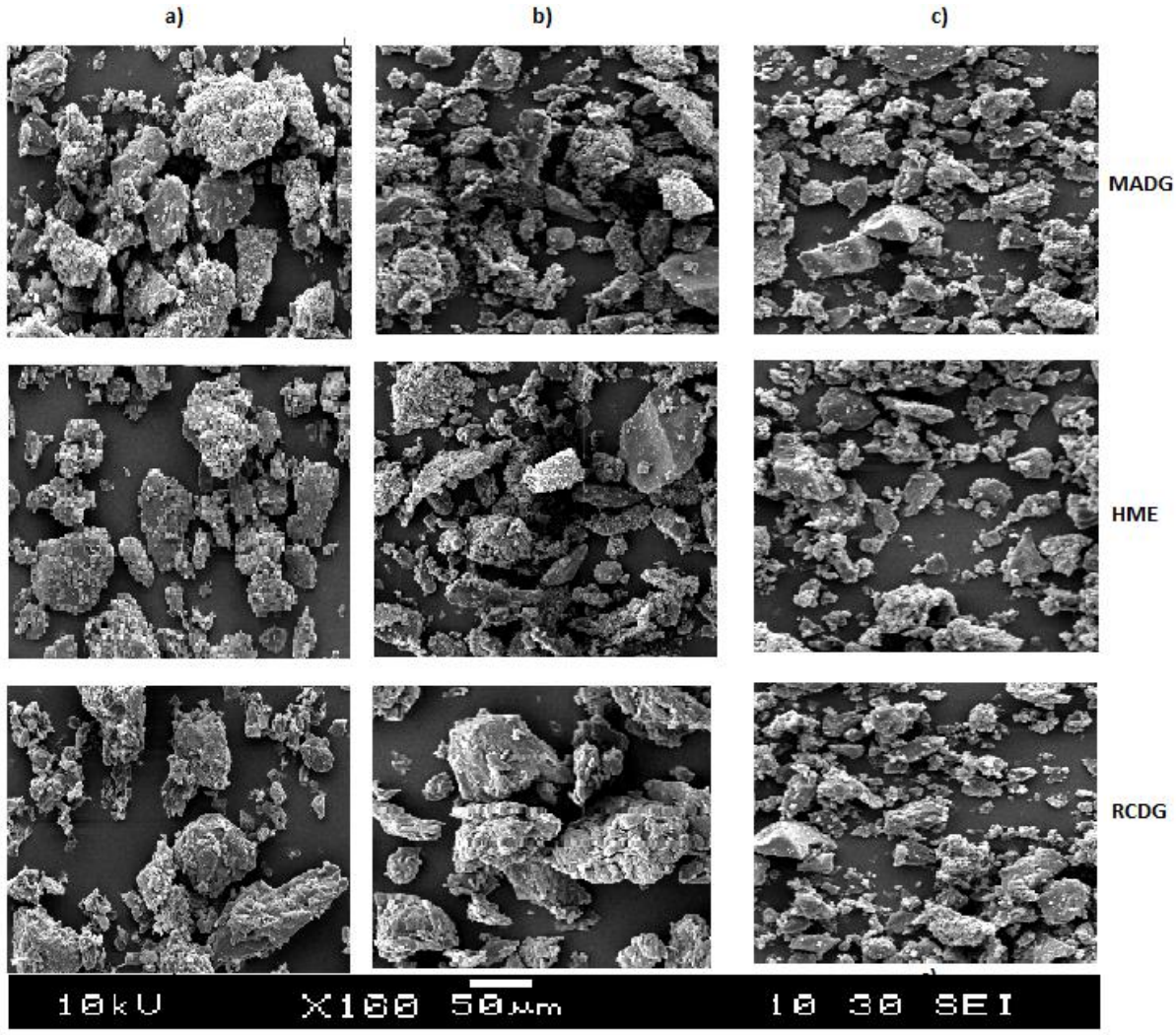


Fig. 2 Particle size distribution of granules.

SEM analysis

The surface morphology of the samples is shown in Fig. 3: the comparison between Maltodextrin/MADG and Maltodextrin/HME granules (Fig. 3) and other granules (Fig. 3) points out that, although the surface appears quite rough and irregular in all granules, Maltodextrin/MADG and Maltodextrin/HME present a more porous surface compared to other granules, and this results in the increase of surface area exposed to the dissolution medium. This supports that Maltodextrin/MADG and Maltodextrin/HME granules were rugged with irregular shape than other granules with smoother surface, specially HPC/ RCDG. Therefore it can be predicted that HPC roller granule should give a slowest release among the examined granules. Fig 3 shows the Acetaminophen content in each fraction of the granules. The results indicate the uniform distribution of the drug in the granules both with maltodextrin and PVP but results in the granules containing Maltodextrin/MADG and Maltodextrin/HME were best. HPC/ RCDG granules gave poor result of drug content because granules were obtained of ununiformed size and high proportions of fines were observed.



SEM images- Granules of Acetaminophen with a) Maltodextrin, b) PVP, c) HPC.

X ray diffraction

It is important to evaluate possible modifications of the physico-chemical properties of drug or polymer and to study possible interactions between the drug and the excipients. Therefore it is important to evaluate the solid state of both the drug and the excipient in the final granules using DSC and XRD. DSC curves of Acetaminophen, polymeric binders, their physical mixture and granules form all three methods are shown in Fig. 4. It indicates that drug and binders remained in its original state in both MADG and RCDG methods. Where as in HME process; the disappearance of the melting endotherm in the DSC scan of extrudes suggested that the drug has been converted to the amorphous form during the process of extrusion.. To confirm this hypothesis, the XRD analysis was performed. Fig. 5 indicates the XRD diffraction patterns of acetaminophen. The characteristics pattern of acetaminophen are present in MADG and RCDG method. They are superimposed to broad singles due to polymeric binder which indicate that drug are in crystalline form. In case of HME formulation confirms the amorphous nature of milled extrudes with no peaks of crystallinity observed.

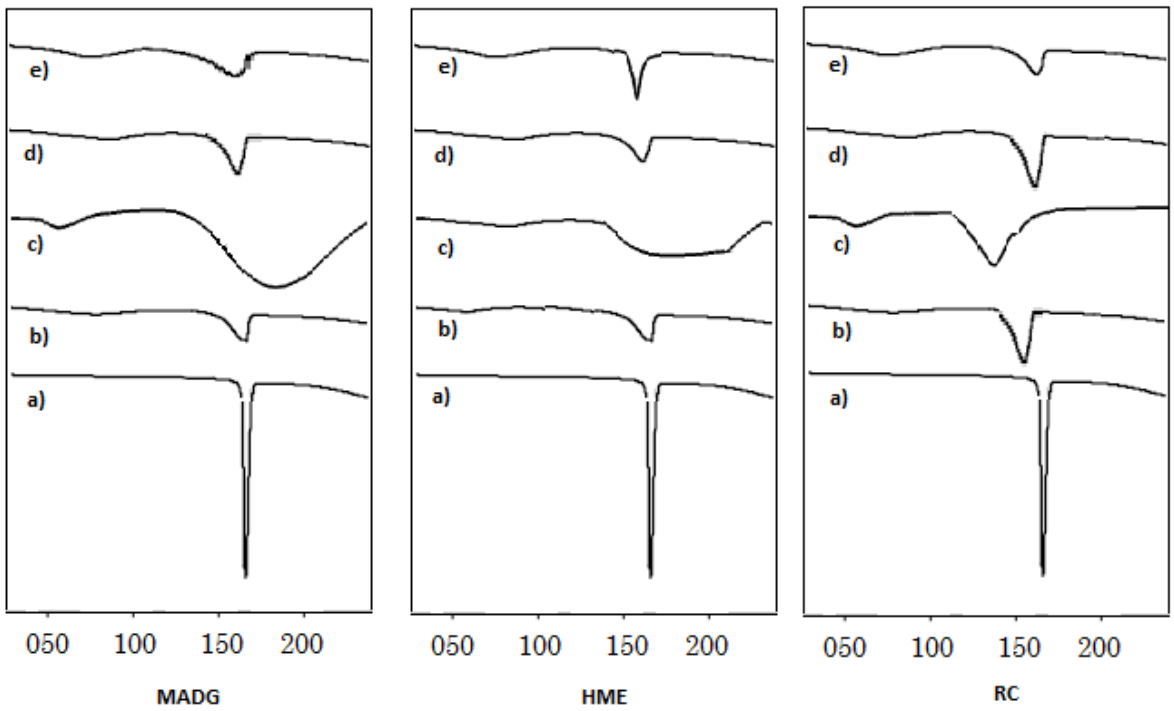


Fig. 4 DSC graph - a) Acetaminophen, b) Physical mixture, c) Acetaminophen:maltodextrin, d) Acetaminophen:PVP, e) Acetaminophen:HPC.

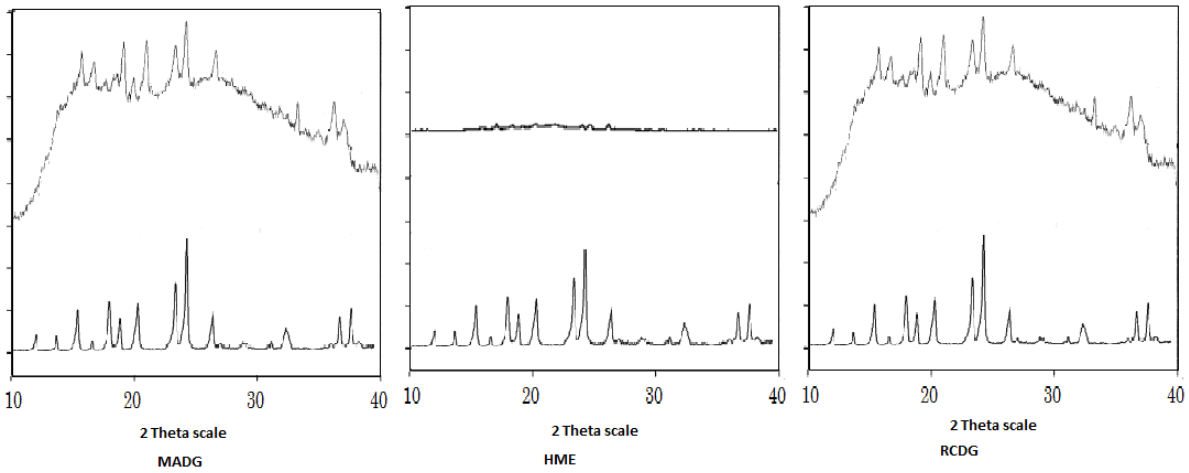


Fig. 5 XRD graph - a)Acetaminophen, b)granules.

Granule strength

The strength of granules was found to be varied significantly in all formulations. Fig. 6 shows the results of attrition impact test for all formulated granulations. HPC-containing granules showed larger weight loss at low impact. Maltodextrin containing granules, were found to be much stronger at all conditions of the impact speed. Whereas PVP showed intermediately results. The results of the impact test indicate that granule strength of formulations with a binder appears to be dominated by properties imposed by a binder rather than constituent API. As previously reported, micromechanical properties of interparticle bridges formed by different binders differ significantly. It could be concluded that for each compound, granules formed with matodextrin were significantly stronger during impact test than granules formed with PVP or HPC [24].

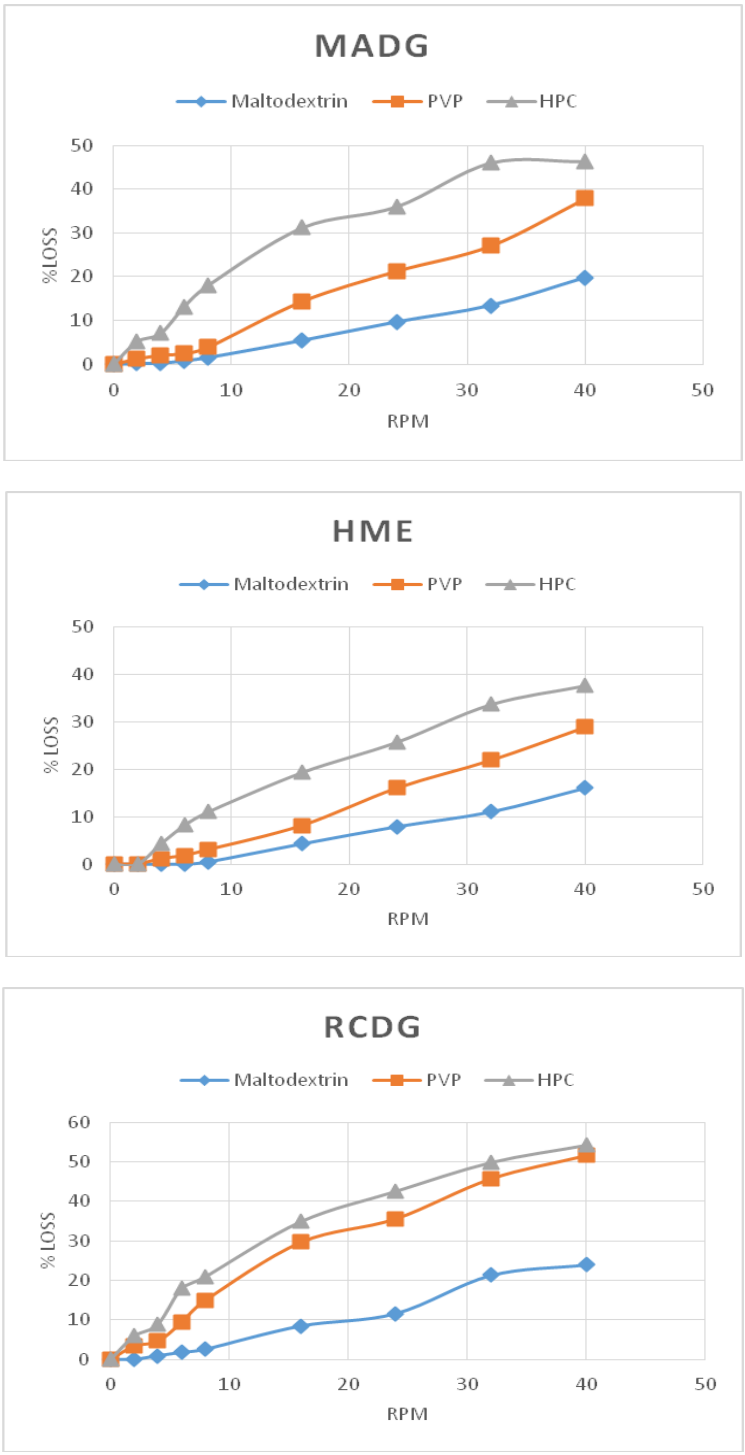


Fig. 6 Granule strength of acetaminophen by different methods.

Preparation and evaluation of tablets

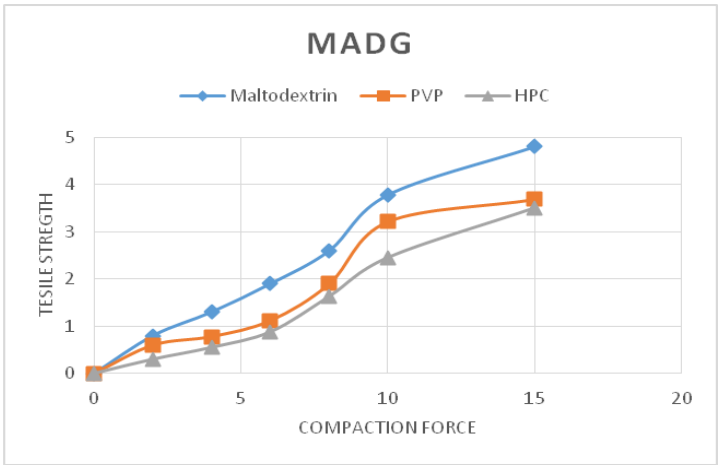
RCDG/ PVP and RCDG/ HPC were not further studied because of high proportion of fines and produced poor compacts. This might be due to elastic deformation of acetaminophen with lower viscosity grade polymeric binder used during compaction[25]. Remaining all formulation gave almost good result. Among them Maltodextrin / MADG and Malltodextrin / HME are best followed by PVP, HPC. Result of evaluation of tablets are shown in table 3.

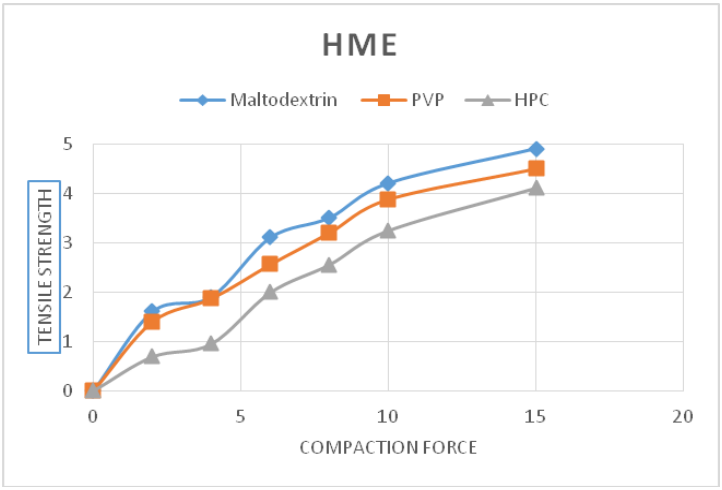
Table 3 Evaluation of different tablets properties.

Method	Binder	Weight (g) (avg.)	Weight % RSD	Thickness (mm) avg.	Thickness % RSD	Hardness (Kg/cm^2)	Hardness % RSD	Mean tablet Assay (%)	% RSD	Disintegration time (min)	Friability (%)
MADG	Maltodextrin	0.60	0.88	6.43	0.09	10.73	1.94	98.23	0.79	3.00	0.12
	PVP K 12	0.59	0.59	6.43	0.09	10.57	0.55	92.20	0.37	3.45	0.18
	HPC	0.55	0.91	6.43	0.09	9.73	2.14	87.67	0.70	4.15	0.20
HME	Maltodextrin	0.60	0.86	5.21	0.05	10.83	1.70	96.73	1.11	5.55	0.81
	PVP K 12	0.65	1.76	5.16	0.11	10.49	1.41	94.43	1.19	6.40	1.20
	HPC	0.59	1.43	5.13	0.14	10.10	0.99	80.13	1.98	6.50	1.48
RC	Maltodextrin	0.58	1.40	5.05	0.21	8.11	2.79	97.37	1.56	6.30	1.11
	PVP K 12	-	-	-	-	-	-	-	-	-	-
	HPC	-	-	-	-	-	-	-	-	-	-

Tensile strength of tablets

Tensile strength of tablets was evaluated as a function of the compression force. The results are shown in fig. 7. A desired tablet tensile strength profile should BE 2.0 MPa or higher at 10 kN compaction force. The maximum tensile strength was relatively high, and the profile had a desired slope. Tablets prepared with PVP and especially maltodextrin containing granules improved the compressibility (Fig.7), For HPC containing granules, the slope of the compactibility was relatively low, so that the desired tensile strength could only be developed at relatively high compaction force. The results revealed that polymeric binders play a vital role in improving compactibility of granules, especially when compactibility of a pure compound is low. Polymeric binders also reduce propensity for sticking [24].





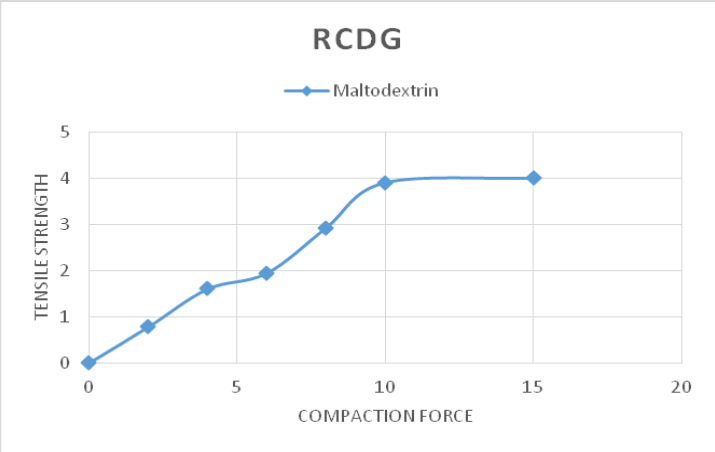


Fig. 7 tensile strength of tablets prepared by different granulation method.

Invitro Dissolution study

In vitro dissolution profiles, pure drug and physical mixtures of Drug/binder were compared (Table 4) The dissolution rate of pure acetaminophen (not shown in table) is quite low because of its crystallinity and poor solubility. In the dissolution profiles, the tablets prepared by Maltodextrin/MADG and Maltodextrin/HME granules shows better release than other granules, confirming that the both Maltodextrin/MADG and Maltodextrin/HME granules with rough surface, therefore with a higher surface area in comparison to other granules therefore 92% amount of drug was found to be dissolved after 30 min for Maltodextrin/ MADG. While Maltodextrin/HME gave 88% release in 30 min.

Invitro dissolution study

Table 4 Invitro dissolution study of prepared tablets.

Method	**Binder**	**% Release in time**			
		15min	%RSD	30min	% RSD
MADG	Maltodextrin	85.87	0.07	92.83	0.14
	PVP K 12	86.23	0.13	90.87	0.07
	HPC	80.40	0.23	85.89	0.29
HME	Maltodextrin	84.73	0.17	88.68	0.09
	PVP K 12	85.28	0.13	86.14	0.10
	HPC	85.29	0.12	86.58	0.11
RC	Maltodextrin	77.81	1.32	87.24	1.20
	PVP K 12	-	-	-	-
	HPC	-	-	-	-

Stability study of tablets

Any significant change in drug content and dissolution study is not observed during stability study of the prepared formulations. It confirms the stability of formulation.

CONCLUSION

The results showed that the MADG and HME technique using maltodextrin, PVP K 12 and HPC as "polymeric-binders" enabled to obtain desirable granules, while the use of RCDG/PVP and RCDG/ HPC gave poor result in granules preparation. MADG/Maltodextrin and HME HME /Malltodextrin provided granules with a more irregular and porous surface area than other granules, as observed by SEM. These characteristics reflected on the dissolution behaviour, showing that granules prepared with Maltodextrin/MADG and Malltodextrin/HME methods increases the dissolution rate of acetaminophen, followed by granules prepared with PVP, HPC in all three granulation methods. In conclusion, the findings of this work showed that MADG and HME methods of granulation could be very successful industry feasible methods to improve the dissolution rate of a poorly soluble drug as Acetaminophen, when associated with maltodextrin as binder. These methods, minimizes the total number of excipients thus decreasing the complexity of the formulation and increasing the scalability of the formulation.

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Abbreviations

HME : Hot melt extrusion
MADG : Moisture assisted dry granulation
RCDG : roller compaction dry granulation
HPC : Hydroxy propyl cellulose
PVP : Polyvinyl pyrrolidone

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