Manipal Journal of Pharmaceutical Sciences

Volume 5 | Issue 2 Article 5

1-9-2019

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Research Article

Development Of Novel Co-Processed Excipients By Spray Drying Method For The Design Of Fast Dissolving Tablets

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Abstract

Co-processed excipients were developed by the spray drying method. In this method, MCC : Aerosil : Fenugreek seed mucilage in different ratios (88:2:10, 90:2:8 and 92:2:6) were used. The prepared excipients were evaluated for compressibility index, that is Carr's index, Hausner's ratio, and flow properties, which is the angle of repose in comparison with physical mixture of the excipients. The angle of repose of co-processed excipients was found to be <30°, which describes a good flow in comparison to the physical mixture of the excipients, due to micronization, a very regular particle size is achieved. Carr's index was found to be in the range of 11.00-13.80% and Hausner's ratio was found to be in the range of 1.00-1.16. Fast dissolving tablets of Repaglinide were prepared using the above novel co- processed excipients and evaluated for pre-compression and post-compression parametres. Among the tablets prepared, the novel co-processed formulations MCC : Aerosil : Fenugreek seed mucilage in 88:2:10 ratio was found to be promising and showed a dispersion time of approximately 37.66 seconds. The wetting time was found to be 35.66 seconds, which facilitated its faster dispersion in the mouth. Stability studies of promising formulations indicated that there were no significant changes in the drug content and *in vitro* dispersion time. IR-spectroscopic studies indicated that there were no drug-excipient interactions. It can be concluded from the present work that novel co-processed excipients used in repaglinide fast dissolving tablets were found to be superior in flow characteristics in comparison with the physical mixture of the same excipients.

Key words: Aerosil, Co-processed Excipients, Fenugreek Seed Mucilage, Microcrystalline cellulose, Repaglinide, Spray drying

Introduction

The major challenge for tablets and capsule manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (>70%) contain excipients at a higher concentration than active drug.[1] In the recent years, drug formulation scientists have identified that single-component excipients cannot always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately.[2] Hence, there is a necessity to have excipients with multiple characteristics built into them such as better flow, no moisture sensitivity, greater compressibility and rapid disintegration ability.[3] One such approach for improving the functionality of excipients is the co-processing of two or more excipients.

Co-processing is based on the novel concept of two or more excipients interacting at the sub-particle level. The main objective of this is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual excipients.[4] Co-processing excipients leads to the formulation of excipient granules with superior properties compared to the physical mixtures of components or individual components.[5] The concept of formulating fast dissolving tablets (FDT) of repaglinide (antidiabetic) using co-processed excipients, which increased the water uptake with

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Date of Submission: 19-June-2019, Date of Revision: 11-Aug-2019 Date of Acceptance: 13-Aug-2019

How to cite this article: Shirsand SB, Aute S, Shailashri, Deshpande R and Amruta. Development Of Novel Co-Processed Excipients By Spray Drying Method For The Design Of Fast Dissolving Tablets. *MJPS* 2019; 5(2): 32-37.

Table 1: Formulations of Repaglinide Fast Dissolving Tablets

	Formulation Code			
Ingredients (mg/tablet)	CP_0	$MCAF_1$	$MCAF_2$	$MCAF_3$
Repaglinide	1	1	1	1
Co-processed Excipients	-	12	12	12
Aspartame	3	3	3	3
Sodium stearyl fumarate	1.5	1.5	1.5	1.5
Talc	3	3	3	3
Pine apple Flavour	1.5	1.5	1.5	1.5
MCC (Avicel PH-102)	30	30	30	30
Mannitol (Pearlitol SD 200)	110	98	98	98
Total Weight	150	150	150	150

CPo-Control formulation (without Co-processed excipients).
MCAF Indicates: Microcrystalline cellulose, Aerosil & Fenugreek seed mucilage.

shortest wetting time and thereby decreased the disintegration time of the tablets by simple and cost effective (at low concentration of excipients) direct compression technique. [6-8]

Materials

Repaglinide was gifted from Torrent Pharmaceuticals, Sikkim Plant. Aerosil was gifted from Alkem Labs Pvt Ltd, Mumbai, India. Fenugreek powder was prepared in HKEs college laboratory. All the other chemicals used were of analytical grade.

Development of Co-Processed Excipients[9]

Development of Co-processed Excipients by Spray Drying Method:

Procedure:

Co-processed excipients were prepared by using spray-drying technique using a laboratory spray dryer (Model SPD-P-111; Technosearch Instruments, India) with a standard 0.7 mm nozzle. Different batches of co-processed excipients were prepared by dissolving the different ratios of polymer MCC : Aerosil : Fenugreek seed mucilage in different ratios (88:2:10, 90:2:8 and 92:2:6) in Dimethylformamide (DMF) under constant stirring at 500 rpm for 2 hours using a magnetic stirrer. When the polymer Dimethylformamide (DMF) solution was fed to the nozzle with a peristaltic pump, the atomization occurred by the force of compressed air, disrupting the Dimethylformamide (DMF) solution into little droplets. The droplets, together with hot air, were blown into the drying chamber, where the solvent in the droplets was evaporated and discharged through an exhaust tube. The co-processed excipients were collected from cyclone one and cyclone two, washed with distilled to remove surface adhered excipients and further dried completely in hot air oven at 40°C for 12 hours and stored in a well-closed container.

The processing conditions of the spray drying were:

Inlet Temperature: 165°C

Outlet temperature: 120°C

Feed pump rate: 2ml/min

Spray pressure atomization: 2×10^5 PC.

Isolation of Mucilage By conventional method[10]:
Seeds were collected and soaked in distilled water for forty eight hours and then boiled for one hour for the complete release of mucilage into the water. The material was then filtered by squeezing it in a muslin cloth to remove marc. An equal volume of acetone was added to the filtrate to precipitate the formed mucilage. The mucilage was collected separately and dried in an oven at temperature less than 60^0C, powdered (# 60) mesh, weighed and stored in an airtight well-closed container until further use.

Preparation of fast dissolving tablets of Repaglinide by direct compression method:
Fast dissolving tablets of Repaglinide were directly compressed according to the formulae given in Table 1. All the ingredients were sifted through 60 mesh separately. The drug and Microcrystallinecellulose were mixed by a little portion of both each time and blending it to get a uniform mixture and kept aside.

Then, the ingredients were weighed and mixed in a geometrical order and the tablets were compressed at 7 mm size to get a tablet of 150 mg weight using a Rotary Clit 10 station compression machine.[11]

Evaluation of Physically mixed Excipients/Co-processed Excipients:

The developed excipients were evaluated for compressibility index (Carr's index), Hausner's ratio and flow properties (angle of repose) in comparison with physical mixture of excipients shown in Table 2.

Evaluation of fast dissolving tablets:

The prepared batches of formulations were evaluated post compression parametres such as drug content uniformity, weight variation, hardness, friability, thickness, *in vitro* dispersion time, *in vitro* drug release and stability studies (given in Table 3).

Weight Variation:

The weight of the prepared tablet was routinely determined to ensure that a tablet contains the proper quantity of the drug. The USP weight variation test is done by collecting 20 tablets at random and weighing them individually, and the individual weights were compared with that of the average weight for the determination of weight variation.[12]

Thickness variation:

The thickness of the tablet is important for the uniformity of tablet size. The thickness was measured using Vernier Calipers. It was determined by measuring the thickness of three tablets of each formulation.

Tablet Hardness and Friability:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage is dependent on its hardness. The hardness of each batch of tablet was checked by using monsanto hardness tester. The hardness was measured in terms of kg/cm^2. Three tablets were chosen randomly and tested for hardness. The average hardness of three tablets was recorded. Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the surface of tablets. Friability generally reflects poor cohesion of tablet ingredients. Ten tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then the tablets were removed from the friabilator, dusted off of the fines and again weighed, and the weight was recorded.

Drug Content Uniformity:

Ten tablets were weighed and powdered, the quantity of powder equivalent to 1 mg of Repaglinide was transferred to a 50 ml volumetric flask and 40 ml methanol was added to the flask. The drug was extracted into the methanol by shaking the flask vigorously for 15 minutes. Then the volume was adjusted to 50 ml with methanol and the liquid was filtered. The Repaglinide content was determined by measuring the absorbance at 237 nm after an appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.[13]

Wetting Time and Water Absorption Ratio:

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete the wetting was measured. The wetted tablet was then weighed (given in Table 3).[14]

Water absorption ratio 'R' was determined using the following equation:

$$R = 100 \times (Wa - Wb|Wb)$$

Where,

W_a = Tablet weight before water absorption,

W_b = tablet weight after water absorption.

***In vitro* Dispersion Time:**

The tablet was added to 10 ml of phosphate buffer solution in a beaker, pH 6.8 at 37±0.5°C. Time required for complete dispersion of the tablet was measured (given in Table 3).[15]

***In vitro* Dissolution Study:**

In vitro dissolution of a Repaglinide FDT was studied in USP type-II dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer pH 6.8 was used as a dissolution

Table 2: Pre-compression Parameters of physically mixed excipients/Co-processed Excipients

Formulation Code						
Parameters	**$PMCAF_1$**	**$MCAF_1$**	**$PMCAF_2$**	**$MCAF_2$**	**$PMCAF_3$**	**$MCAF_3$**
Bulk density (g/cc)	0.45	0.50	0.45	0.51	0.45	0.51
Tapped density (g/cc)	0.55	0.57	0.55	0.58	0.53	0.60
Angle of repose (degree)°	27.75	23.91	28.39	24.00	28.65	24.17
Carr's index (%)	18.21	11.96	18.91	12.10	18.72	13.80
Hausner's Ratio	1.22	01.13	1.22	01.14	1.23	01.16

Table 3: Post-compression Parameters of Repaglinide Fast Dissolving Tablet formulations.

Parameters→ Formulation Code ↓	**Hardness (kg/cm^2)* ±SD**	**Friability (%)**	**Thickness* (mm**	***In vitro* dispersion time (s)* ±SD**	**Wetting time (s)* ± SD**	**Water absorption ratio (%)* ±SD**	**Percent drug content (%)* ±SD**	**Weight variation (%)**
CP_O	2.5±0.10	0.33	2.60±0.17	122±4.35	115±2.00	56.86±1.40	99.45±0.01	142-158 mg (IP limits ± 7.5%)
$MCAF_1$	2.55±0.05	0.63	2.43±0.15	37.66±1.52	35.66±1.53	85.63±0.60	99.35±0.79	
$MCAF_2$	2.61±0.70	0.67	2.60±0.17	43.00±3.05	41.00±4.35	83.67±1.40	99.28±2.02	
$MCAF_3$	2.56±0.07	0.67	2.76±0.15	44.66±4.16	39.66±2.08	80.95±2.05	99.35±1.57	

*Average of three determinations

Table 4: Comparative in vitro Dissolution parameters of control, commercial and promising formulations in pH 6.8 Phosphate Buffer

	parameters						
	D_5	**D_{10}**	**D_{15}**	**$t_{50\%}$**	**$t_{70\%}$**	**$t_{90\%}$**	**DE_{10min}**
CP_0	27%	50%	57%	10 min	>30 min	>30 min	26.69%
$MCAF_1$	55%	84%	91%	4.2 min	7.6 min	14 min	53.03%
CCF	26%	50%	56%	10 min	>30 min	>30 min	25.21%

CP0 is control formulation, MCAF1 is promising fast dissolving tablet formulation, CCF is conventional commercial tablet formulation, D5 is percent drug released in 5 minutes, D10 is percent drug release in 10 minutes, D15 is percent drug release in 15 minutes, DE10 min is dissolution efficiency at 10 minutes, t50% is time for 50% drug dissolution, t70% is time for 70% drug dissolution, t90% is time for 90% drug dissolution.

medium. The stirrer was adjusted to rotate at 50 rpm. The dissolution media was previously warmed to 37±0.5ºC and was maintained same throughout the experiment. One tablet was used in each test. 5 ml of the sample of dissolution medium were withdrawn by means of a syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 241 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Repaglinide released was calculated and plotted against time. For comparison, the dissolution of Repaglinide from commercial formulation was also studied.

Accelerated Stability Studies:

Promising formulation stability studies ($MCAF_1$) was carried out by storing 15 tablets in an amber coloured screw capped bottle at an elevated temperature of 40ºC/ 75% RH over a period of three months. At an interval of 1 month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

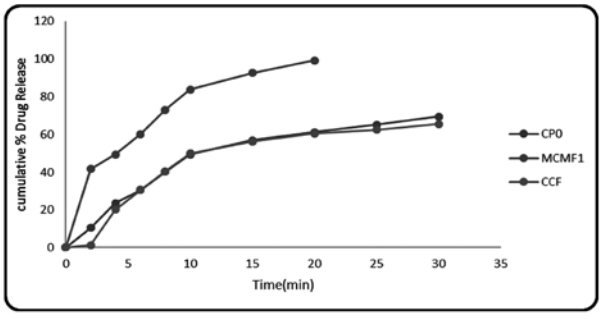

Figure 1: Comparative cumulative percent drug release versus time plot (zero order) of control formulation, promising tablet formulations of Repaglinide and Commercial Conventional Formulation CCF in phosphate buffer pH 6.8

CCF..... Commercial conventional formulation
FDT..... Fast dissolving tablet
MCC..... Microcrystalline cellulose
min..... Minutes
rpm..... Revolutions per minute
s..... Seconds
SD..... Standard deviation

Results and Discussion

Co-processed excipients were prepared by spray drying using co-processed excipients MCC : Aerosil : Fenugreek seed mucilage in different ratios (88:2:10, 90:2:8 and 92:2:6). The co-processed excipients were evaluated for their flow and compression properties in comparison with physical mixture of excipients. The angle of repose of co-processed excipients was found to be <30°, which indicated an excellent flow in comparison to the physical mixture of excipients (near to 30°) due to granule formation, Carr's index in the range of 11.00-13.80% and Hausner's ratio in the range of 1.00-1.16 (Table 2).

Fast dissolving tablets of Repaglinide were prepared using above co-processed excipients. A total of three formulations and the control formulation CP_0 (without excipients) were developed. As the blends were free flowing (angle of repose <30 and Carr's index <15 % Table 2), tablets obtained were of uniform weight (due to uniform die fill), with acceptable variations as per IP specification i.e., below 7.5%. The drug content was found to be in the range of 99.28 to 99.35%, which is within acceptable limits. The hardness of the tablets was found to be in the range of 2.55-2.61 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of excipients to swell in presence of little amount of water, were found to be in the range of 80.95-85.63% and 35.66-41.00 seconds, respectively. Among the tablets prepared, co-processed formulations $MCAF_1$ containing MCC : Aerosil : Fenugreek seed mucilage in different ratios (88:2:10) were found to be promising and showed an *in-vitro* dispersion time of 37.66 seconds, wetting time of 35.66 seconds, and water absorption ratio of 85.63% and control formulation (CP_0) showed 122 seconds, 115 seconds, and 56.86% values, respectively for the above parametres (Table 3). *In-vitro* dissolution studies on the promising formulation $MCAF_1$, control (CP_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parametre values viz., percent drug dissolved in 5, 10 and 15 minutes (D_5, D_{10} and D_{15}), dissolution efficiency at 10 minutes (DE_{10} min), $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in Table 4 and the dissolution profile depicted in Figure 1. This data reveals that overall, the formulation $MCAF_1$ has shown about nearly two and a half fold faster drug release when compared to the commercial conventional tablet formulation of Repaglinide ($t_{50\%}$ in 4.20 min). IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of $MCAF_1$ showed all the characteristic peaks of Repaglinide pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Stability studies of the above formulations indicated that there are no significant changes in the drug content and *in vitro* dispersion time at the end of the three-month period ($p<0.05$).

Conclusion

Repaglinide tablets containing co-processed excipients exhibited good flow and compression characteristics. Repaglinide tablets containing co-processed excipients exhibited quick disintegration and improved drug dissolution. It can be concluded from the present work that co-processed excipients of MCC, Aerosil and Fenugreek seed mucilage are superior to physical mixture of MCC, Aerosil and Fenugreek seed mucilage. The developed co-processed excipients may be used in future research for the development of novel solid dosage forms.

Acknowledgement

The authors are thankful to Torrent Pharmaceuticals, Sikkim Plant, India, for providing a gift sample of Repaglinide. The authors are also thankful to Alkem Labs Pvt Ltd, Mumbai, Maharashtra, India, for providing a gift sample of Aerosil and Microcrystalline cellulose, respectively. The authors are very grateful to the management and staff of H.K.E. Society's College of Pharmacy, Gulbarga, Karnataka, for providing facilities to carry out the work.

Conflict of interest- None

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