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Development and Evaluation of a Directly Compressible Co-processed Multifunction Sustained Release Agent for Gliclazide Sustained Release Tablets

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Abstract:

Directly compressible co-processed sustained release multifunction agent [DCCSRA] comprising povidone and glyceryl behenate in the ratio of 1:1, 1:2 and 1: 3 were prepared and evaluated. The DCCSRA exhibited good flow and compressibility. The DCCSRA served as a retardant, binder and lubricant in Gliclazide sustained release tablets. By optimization of DCCSRA quantity in formulation, the drug release pattern of the trial formulation was made similar to the release pattern of the reference product of Gliclazide (GLIZID MR 30).

Keywords: *Glyceryl behenate; Povidone; Coprocessing; Gliclazide; Sustained Release; Dissolution*

Introduction:

Co-processed excipients are combinations of two or more excipients that possess performance advantages when compared to a physical mixture of the same combination of excipients. Typically co-processed excipients are produced using some form of specialized manufacturing process and are helpful in achieving the desirable characteristics in a formulation. [1-7]

This work focuses on the preparation and evaluation of a co-processed excipient comprising povidone and glyceryl behenate. This co-processed excipient is useful as a sustained release matrix forming agent.

Glyceryl behenate is mainly used as tablet and capsule lubricant and as tablet binder. It has been used in preparation of sustained release tablets and as matrix-forming agent (above 10 % w/w) for the controlled release of water soluble drugs.

Povidone is used as binder (at a concentration of 0.5% w/w to 5 % w/w) in tablets. It also acts as a solubiliser and enhances the dissolution of poorly soluble drugs from solid dosage forms. The molecular adduct formation of povidone may be used to advantage in slow release solid dosage forms. [8]

The co-processing of glyceryl behenate with povidone by hot melting and co-precipitation leads to formation of a multifunctional excipient which can act as a matrix forming agent, binder and lubricant. This improved functionality of the co-processed excipient may reduce the time and cost of manufacture of sustained release tablets.

Glyceryl behenate has been used as matrix forming agent in formulation of sustained release tablets of water soluble drugs. Since glyceryl behenate is hydrophobic, the hydrophobicity gets reduced when co-processed with povidone which is hydrophilic. To check the suitability of DCCSRAs for sustained release of water insoluble drug, gliclazide was selected as the drug candidate in this work.

Materials and Methods:

Materials

Glyceryl Behenate (Compritol 888), Povidone K 25, Dicalcium Phosphate Dihydrate (Emcompress), Lactose Monohydrate (Flowlac 100), Gliclazide was received from Micro Labs Ltd. (Bangalore, India).

Methods:

The following experimental approach has been used in this work.

1. Preparation of physical blend of glyceryl behenate and povidone and evaluation of its flow property
2. Preparation of DCCSRA mixtures of glyceryl behenate and povidone

comprising different ratios of the two components by hot melting method and coprecipitation method and evaluation of the flow of the DCCSRAs

3. Preparation of the Gliclazide sustained release tablets using the DCCSRAs and comparison of the drug release pattern with that of a reference product [Glyzid MR 30]

The flow characteristics of the physical blend of glyceryl behenate and povidone has been compared with that of the co-processed excipient. The co-processed excipient was evaluated for its suitability for direct compression of Gliclazide sustained release tablets.

Preparation of Physical Blend of Glyceryl behenate and Povidone

Povidone and glyceryl behenate were blended in the ratio of 1:1, 1: 2 and 1: 3 in a lab scale double cone blender.

Preparation of Directly compressible co-processed sustained release multifunctional agents by Hot melting Method [DCCSRA-HM]

DCCSRA-HMs were prepared by hot melting method. Glyceryl behenate and povidone were passed through 40-mesh sieve, mixed well and heated to about 90°C in a stainless steel vessel on a water bath with stirring to obtain a smooth paste which was then cooled to room temperature with intermittent mixing. The mass was then milled in a multimill with 1.5mm screen and passed through 30-mesh sieve and stored in an airtight container till further use. The ratio of the components in the co-processed excipients have been presented in Table 1.

Preparation of Directly compressible co-processed sustained release multifunctional agents by Co-precipitation method [DCCSRA-CM]

DCCSRA-CMs were prepared by coprecipitation method. Glyceryl behenate and povidone were passed through 40-mesh sieve, mixed well and 50g of the mix was dissolved in 250ml of methylene chloride in a beaker by stirring . The temperature was maintained between 40°C and 45°C, and stirring was continued till most of methylene chloride has been evaporated. The wet coherent mass was granulated through 30-mesh sieve, dried in a tray drier at 45°C for 15 minutes. The dried granules were sifted through 30-mesh sieve and stored in an airtight container till further use. The ratio of the components in the co-processed excipients have been presented in Table 1

Evaluation of Angle of repose

For the measurement of angle of repose, a glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was passed through the funnel until the apex of the conical pile touched through the funnel. The angle of repose was calculated with formula $\tan \alpha = H/R$, where α is the angle of repose and R is the radius of the conical pile.

The angle of repose of the physical blend and co-processed excipient were measured by the above method. The results have been tabulated in Table 2.

Preparation and Evaluation of Gliclazide sustained release tablets

Gliclazide sustained release tablets were prepared by direct compression. Gliclazide, DCCSRA-HM/ DCCSRA-CM and Emcompress / Flowlac 100 were passed through 30 mesh sieve and then blended. The angle of repose of the blends was measured as described above. (Table 2). The tablets were compressed with a target weight of 150 mg using 7 mm normal concave punches using an 8 station tablet machine (Rimek). The composition of various trial formulations formulated with the DCCSRA have been presented in the Table 3, the crushing strength, friability and angle of repose in Table 4 and drug release pattern in Table 5.

The Gliclazide release was estimated by HPLC method. A mixture of 0.1 volumes of Triethylamine, 0.1 volumes of Trifluoroacetic acid, 45 volumes of Acetonitrile and 55 volumes of water was used as the mobile phase. A flow rate of 2 ml/minute and a detection wavelength of

Table 1: DCCSRA – Ratio of the Components

Hot Melting Method		
Composition		Ratio
Composition-I	[DCCSRA-HM-I]	Povidone : Glyceryl Behenate [1:1]
Composition-II	[DCCSRA-HM-II]	Povidone : Glyceryl Behenate [1:2]
Composition-III	[DCCSRA-HM-III]	Povidone : Glyceryl Behenate [1:3]
Co-precipitation method		
Composition-I	[DCCSRA-CM-I]	Povidone : Glyceryl Behenate [1:1]
Composition-II	[DCCSRA-CM-II]	Povidone : Glyceryl Behenate [1:2]
Composition-III	[DCCSRA-CM-III]	Povidone : Glyceryl Behenate [1:3]

Table 2: Evaluation of Flow Property [Angle of Repose] of the Physical Blend and DCCSRA

Composition	Angle of Repose		
	Physical Blend	DCCSRA-HM	DCCSRA-CM
Composition-I	40°	23°	21°
Composition-II	42°	25°	23°
Composition-III	45°	28°	26°
Pure Povidone K 25		35°	
Pure Glyceryl behenate		43°	

235nm were selected for the estimation. A C18, 250mm x 4.6 mm, 5µm HPLC column (Thermo Scientific BDS Hypersil) was used. The Dionex HPLC system model P680A LPG 4 was used and the data was processed using the Chromeleon software.

Evaluation of reference product of Gliclazide sustained release tablets [Glizid MR 30]

The *in vitro* dissolution release of the reference product (Glizid MR 30 tablet) was estimated as described above in different dissolution media (Table 6)

Results:

Physical properties of glyceryl behenate, povidone K 25 and the physical blend of glyceryl behenate with povidone K 25

The angle of repose of pure glyceryl behenate, pure povidone K 25 and the physical blend have been presented in Table 2.

The angle of repose values of the physical blend ranging from 40 ° to 45 ° indicate that the flow property of the physical blend may not be suitable for direct compression. The angle of repose values of the DCCSRA-HM and DCCSRA-CM between 21 ° to 28 ° indicate that the DCCSRAs have a good flow suitable for use in direct compression process. (Table 2)

Evaluation of Gliclazide tablets compressed with DCCSRA-HMs and DCCSRA-CMs

To investigate the versatility of the DCCSRA-HMs and DCCSRA-CMs, tablets of Gliclazide were prepared and evaluated for crushing strength, friability and in vitro dissolution release. Initially batches HG1 to HG3 and CG1 to CG3 were formulated to assess the flow of the blend, lubrication capacity, binding capacity (crushing strength) and the retarding capacity of the DCCSRA-HMs & DCCSRA-CMs.

The concentration of Gliclazide was kept constant at 30 mg (20 % w/w) in all the batches. (Table 3). The concentration of DCCSRA-HM used was 75 mg (50% w/w) in the three batches of HG1 to HG3 and concentration of DCCSRA-CM used was 150 mg (50% w/w) in the three batches of CG1 to CG3. The diluent used in these batches was lactose (Flowlac 100)

Table 3: Composition of Gliclazide sustained release tablets using DCCSRA- HM and DCCSRA- CM [Trials]

Materials	Batch Code													
	HG1	**HG2**	**HG3**	**HG4**	**HG5**	**HG6**	**HG7**	**CG1**	**CG2**	**CG3**	**CG4**	**CG5**	**CG6**	**CG7**
Gliclazide	30	30	30	30	30	30	30	30	30	30	30	30	30	30
DCCSRA- HM-I	75				22.5	30	33							
DCCSRA -HM-II		75												
DCCSRA- HM-III			75	75										
DCCSRA- CM-I								75				22.5	30	33
DCCSRA -CM-II									75					
DCCSRA- CM-III										75	75			
Flowlac 100	45	45	45		97.5	90	87	45	45	45		97.5	90	87
Emcompress				45							45			

Table 4: Evaluation of Blend and Tablets of Gliclazide compressed with DCCSRA-HM and DCCSRA-CM

Parameters	Gliclazide Tablets Batch Code													
	HG1	**HG2**	**HG3**	**HG4**	**HG5**	**HG6**	**HG7**	**CG1**	**CG2**	**CG3**	**CG4**	**CG5**	**CG6**	**CG7**
Angle of repose	22°	24°	27°	28°	23°	25°	26°	23°	24°	28°	28°	24°	26°	27°
Crushing strength	97N	88N	85N	82N	95N	92N	90N	95N	84N	83N	81N	93N	90N	88N
Friability	0.08%	0.10%	0.13%	0.15%	0.08%	0.09%	0.07%	0.10%	0.11%	0.13%	0.16%	0.12%	0.13%	0.13%

Table 5: Drug release of Gliclazide from trial formulations HG1 to HG4 and CG1 to CG4

Time in Hours	% Mean Drug Release in pH 7.4 phosphate buffer *							
	HG1	HG2	HG3	HG4	CG1	CG2	CG3	CG4
1	6	7	6	5	5	6	6	6
2	10	11	10	7	11	11	10	8
4	15	16	14	11	14	15	13	11
6	19	20	18	13	20	21	19	14
8	23	23	21	14	24	23	20	15
10	26	26	24	16	27	26	23	16
12	29	29	27	17	30	29	26	18

* USP dissolution test apparatus fitted with paddle rotating at 50 rpm. 900 ml of pH 7.4 buffer per vessel

at a concentration of 45mg (30% w/w) in each batch.

The crushing strength of the tablets was found to be maximum for tablets compressed with DCCSRA (povidone: glyceryl behenate [1:1]) when compared to the tablets compressed with DCCSRA with lesser quantities of povidone (Table 4).

The in-vitro dissolution profile in Table 5 show that the dissolution release decreases with increase in the concentration of Glyceryl behenate in the DCCSRA-HM and DCCSRA-CM. The release at each time point was highest with excipient of ratio 1:1 and lowest with ratio of 1:3. (Table 5).

Effect of Lactose and Dicalcium Phosphate in Gliclazide Drug Release

The batches HG3 and HG4 were formulated using the DCCSRA-HM [Povidone: Glyceryl behenate: 1: 3] and batch CG3 and CG4 were formulated using the DCCSRA-CM [Povidone : Glyceryl behenate : 1: 3]. In batch HG3 and CG3 Lactose (Flowlac 100) was used as diluent and in batch HG4 and CG4 dicalcium phosphate (Emcompress) was used as diluent. (Table 5)

Evaluation of Dissolution profile of Gliclazide Reference Product (Glizid MR 30 tablet) and Trial Formulations

To match the dissolution profile of test product with that of the reference product, the trial batches of HG5 to HG7 and CG5 to CG7 were formulated by varying the concentration of co-processed multifunctional sustained release agent. The DCCSRA-HM of povidone : glyceryl behenate (1:1) was used for trials HG5 to HG7 and The DCCSRA-CM of povidone : glyceryl behenate (1:1) was used for trials CG5 to CG7. The tablet weight was kept constant at 150 mg and the difference in the concentration of DCCSRA was adjusted with Lactose (Flowlac 100). The dissolution release in different media have been presented in Table 6.

Discussion:

In the present study the DCCSRAs were prepared and the feasibility of using the co-processed agent as multifunctional agent in a sustained release formulation was evaluated by comparing the in vitro dissolution release of the trial formulations containing Gliclazide with that of reference product (Glizid MR 30 tablet)

The angle of repose of physical blends of povidone K 25 and glyceryl behenate (containing the components in the ratios 1:1,1:2 and 1:3) were found to be 40°, 42° and 45° respectively indicating that the flow of the blend has to be improved if the blend has to be used for direct compression .

The angle of repose of DCCSRA-HMs of povidone K 25 and glyceryl behenate were 23°, 25° and 28° respectively (Tables 1 and 2). The angle of repose of DCCSRA-CMs of povidone K 25 and glyceryl behenate were 21°, 23° and 26° respectively (Table 2). These angle of repose values show that the DCCSRAs have better flow than the physical blend of povidone and glyceryl behenate.

Table 6: Dissolution release values of Gliclazide trials HG5, HG6, HG7, CG5, CG6, CG7 and reference product Glizid MR 30 tablet in different dissolution media & difference factor (f1) and similarity factor (f2)

Time in Hours	% Mean Drug Release						
	pH 4.5 Acetate Buffer						
	HG5	**HG6**	**HG7**	**CG5**	**CG6**	**CG7**	**Glizid**
1	18	15	12	19	14	11	8
2	26	25	22	26	26	23	17
4	45	43	41	44	44	42	37
6	67	64	61	68	66	60	58
8	80	75	72	82	76	71	70
10	91	87	81	93	85	82	78
12	100	95	89	99	96	88	85
f1	21.25	14.45	7.08	22.1	15.3	6.8	
f2	47.79	56.13	70.91	47	54.97	70.39	

Time in Hours	% Mean Drug Release						
	pH 7.4 phosphate buffer						
	HG5	**HG6**	**HG7**	**CG5**	**CG6**	**CG7**	**Glizid**
1	20	16	13	22	15	12	10
2	28	24	21	29	24	20	17
4	49	42	36	50	43	34	35
6	70	65	55	72	64	56	53
8	82	76	74	84	78	73	68
10	93	89	85	95	90	86	83
12	100	98	93	99	97	95	91
f1	23.81	14.85	5.6	26.33	15.13	5.88	
f2	45.19	55.19	73.42	42.91	54.77	73.55	

The angle of repose values of the Gliclazide trial formulation blends have been presented in Table 4. These values below 30° indicate the good flow of these blends which is suitable for direct compression. The results of crushing strength and friability of trial batch tablets reveal that the co-processed agent provides sufficient strength to the tablets. (Table 4)

The Gliclazide batches HG4 and CG4 were formulated with dicalcium phosphate (Emcompress) which is an insoluble diluent and the batches HG3 and CG3 was formulated with lactose (Flowlac 100) which is a soluble diluent.

The in vitro dissolution release of HG3 and CG3 batches was higher at all the time points when compared with HG4 and CG4 batches (Table 5).

This shows that the dissolution release increases when a soluble excipient is used in the formulation along with the proposed DCCSRA.

The f1 and f2 results (Table 6) of Gliclazide tablets show that the dissolution release pattern of the trial batches HG7 and CG7 were similar to that of reference product (Glizid MR 30) in two dissolution media.

Conclusion:

In the trial formulations using direct compression, the Gliclazide was directly compressed using DCCSRA and lactose (Flowlac 100). The process of direct compression was simple with two additives leading to saving of cost and time. The DCCSRA used in the formulation acted as retardant, binder and lubricant. No glidant was used to assist the flow of blend during compression.

The calculated difference factor (f1 factor) and similarity factor (f2 factor) of Gliclazide trial batch HG7 and CG7 show that the dissolution release pattern of these batches were comparable to that of reference product (Glizid MR 30). [9,10]

The above facts suggest that the DCCSRAs which have been prepared and evaluated in this study may be used as a multifunctional excipient in the sustained release formulation of water insoluble drug such as Gliclazide tablets.

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References:

[1] Mukesh C. Gohel, Rajesh K. Parikh, Bansari K. Brahmbhatt, and Aarohi R. Shah. AAPS PharmSciTech 2007; 8 (1) Article 9.

[2] Nahala S. Barakat, Ibrahim M, Elbagory, and Alanood S. Almurshedi. Drug Delivery 2009; 16(1):57-65.

[3] Vasinee Limwong, Narueporn Sutanthavibul, and Poj Kulvanich. AAPS PharmSciTech 2004; 5 (2) Article 30.

[4] Mukesh C. Gohel, Rajesh K. Parikh, Bansari K. Brahmbhatt, and Aarohi R. Shah. AAPS PharmSciTech. 2007; 8 (1) Article 13.

[5] Jacob.S, Shirwaikar. A.A., Joseph. A, Srinivasan. K.K. Indian Journal of Pharmaceutical Sciences. 2007; September – October.

[6] Arvind K. Bansal, Satish K Nachaegari. Pharmaceutical Technology. January 2004; 52-64.

[7] Gohel .M.C., Pranav D Jogani. J Pharm Pharmaceut Sci 2005; 8(1): 76-93.

[8] Raymond C Rowe, Paul J sheskey and Paul J Weller. Hand Book of Pharmaceutical Excipients. Published by the Pharmaceutical Press and the American Pharmaceutical Association, Fourth Edition 2003.

[9] United States Pharmacopoeia and National Formulary (USP 31-NF26). Rockville, MD: US Pharmacopoeia 2008.

[10] Vinod P. Shah, Yi Tsong, Pradeep Sathe and Roger L. Williams. Office of Pharmaceutical Science, Centre for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD. Available at: http://www.dissolutiontech.com/DTresour/899Art/DissProfile.html.