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Research Article

DEVELOPMENT AND EVALUATION OF A DIRECTLY COMPRESSIBLE CO-PROCESSED MULTIFUNCTION SUSTAINED RELEASE AGENT FOR TABLETS

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ABSTRACT

The aim of the present investigation was to prepare and evaluate directly compressible co-processed sustained release multifunction agent [DCCSRA] comprising povidone and glyceryl behenate. Tramadol HCl sustained release tablets were prepared by direct compression technique using DCCSRA and dicalcium phosphate (Emcompress). The DCCSRA exhibited good flow and compressibility and it served as a retardant, binder and lubricant in Tramadol HCl sustained release tablets. Tramadol HCl dissolution release pattern of the trial formulation was made similar to the release pattern of the reference product (Zydol SR 100 mg tablet) by optimizing the quantity of DCCSRA in formulation. The calculated difference factor (f1 factor) and similarity factor (f2 factor) of trial batch T6 and T7 showed that the dissolution release pattern of these batches were comparable to that of reference product. The results of the accelerated stability of trial batch T7 for 6 months revealed that no significant changes were found in the formulation when it was stored in accelerated condition.

Keywords: Glyceryl behenate, Povidone, Coprocessing, Tramadol HCl, Sustained Release,Dissolution.

INTRODUCTION

In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured in a satisfactory manner. One of the approaches to address the problem was the use of the combination excipients introduced by excipient manufacturers in formulations. Combination excipients fall into two broad categories: physical mixtures and co-processed excipients.

Physical mixtures, as the name suggests, are simple admixtures of two or more excipients typically produced by short duration low-shear processing. They may be either liquids or solids. 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[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 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.

Since povidone is hydrophilic, the hydrophobicity of glyceryl behenate gets reduced when co-processed with povidone. To check the retention capacity of the DCCSRA, the drug molecule selected need to have a high solubility. For this study, Tramadol HCl was selected as a model drug based on this solubility criterion.

MATERIALS AND METHODS

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

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 and evaluation of the flow of the DCCSRAs
3. Preparation of the Tramadol HCl sustained release tablets using the DCCSRAs
4. Evaluation of the Tramadol HCl release pattern from tablets prepared with DCCSRA and comparison of the release data with that of a reference product [Zydol SR 100 mg tablet]

The flow property 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 Tramadol HCl 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 multifunction agents [DCCSRA]

DCCSRAs were prepared by hot melting method. Glyceryl behenate and povidone were passed through 40-mesh sieve and mixed well. This powder mix was taken in a stainless steel vessel and heated to about 90°C in a water bath with stirring until a smooth paste was formed. In this mix Glyceryl behenate melts since its melting range is between 65-77°C. This mass was then cooled to room temperature with intermittent mixing. The mass was then milled in a multimill with 1.5mm screen and passed through mesh # 30. The ratio of the components in the co-processed excipients has been presented in Table 1.

Table 1: Table shows DCCSRA – ratio of the components

Composition	Ratio
Composition-I	Povidone : Glyceryl Behenate [1:1]
Composition-II	Povidone : Glyceryl Behenate [1:2]
Composition-III	Povidone : Glyceryl Behenate [1:3]

Evaluation of angle of repose

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 poured through the funnel until the apex of the conical pile touched through the funnel. The angle of repose was calculated with formula tan α = 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 Tramadol HCl sustained release tablets

Tramadol HCl sustained release tablets were prepared by direct compression technique. Tramadol HCl, DCCSRA and Emcompress / Flowlac 100 were passed through 30 mesh sieve and then blended. The angle of repose of the blend was measured as described above [Table 2]. The tablets were compressed with a target weight of 300 mg using 9 mm normal concave punches using an 8 station tablet machine (Rimek). The composition of various trial formulations formulated with DCCSRA has been shown in the Table 3.

The tablets were evaluated for crushing strength, friability and *in-vitro* dissolution release. Crushing strength of the tablets was measured using Dr Schleuniger Pharmatron Tablet tester. Friability was evaluated as the percentage weight loss of 20 tablets tumbled in a friabilator (Model EF2, Electrolab, India) for 4 minutes at 25 rpm.

The i*n-vitro* drug release study of Tramadol HCl was performed using a USP dissolution test apparatus (model TDT-08L, Electrolab) fitted with baskets (75 rpm) at 37±0.5°C using 900 ml of 0.1N hydrochloric acid as dissolution medium. The samples of 10 ml volume were withdrawn at 1, 2, 4, 6, 8, 10 & 12 hours and filtered through 0.45 µm membrane filter[9].

Table 2: Table shows evaluation of flow property [angle of repose] for the physical blend and DCCSRA

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

Table 3: Table shows formulation composition of Tramadol HCl sustained release tablets [Trials]

Materials	Batch Code						
	T1	T2	T3	T4	T5	T6	T7
Tramadol HCl	100	100	100	100	100	100	100
DCCSRA- Composition-I	150	-	-	-	-	-	-
DCCSRA -Composition-II	-	150	-	-	-	-	-
DCCSRA- Composition-III	-	-	150	150	60	75	90
Flowlac 100	-	-	-	50	-	-	-
Emcompress	50	50	50		140	125	110

Tramadol HCl release was estimated by HPLC method. A mixture of 705 ml of acetonitrile and 295 ml of 0.2% v/v trifluoroacetic acid was used as mobile phase. A flow rate of 1 ml/minute and a detection wavelength of 271 nm were selected for the estimation. A C18, 250 mm x 4.6 mm, 5 µ HPLC column of Waters [Symmetry] 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 Tramadol HCl sustained release tablets [Zydol SR 100 mg tablet]

The *in-vitro* dissolution release of the reference product [Zydol SR 100 mg tablet] was evaluated as described above in different dissolution media.

RESULTS

Flow property 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 has been presented in Table 2.

The angle of repose values of the physical blend ranging from 40 º to 45 º indicates that the flow property of the physical blend may not be suitable for direct compression.

The angle of repose values of the DCCSRA between 23 º to 28 º indicates that the DCCSRA have a good flow and it is suitable for use in direct compression process.

Evaluation of Tramadol HCl tablets compressed with DCCSRAs

To investigate the versatility of the DCCSRAs, tablets of Tramadol HCl were prepared and evaluated for crushing strength, friability and *in-vitro* dissolution release. Initially batches T1 to T3 were formulated to assess the flow of the blend, lubrication capacity, binding capacity (crushing strength) and the retarding capacity of the DCCSRAs.

The concentration of Tramadol HCl was kept constant at 100 mg (33.33% w/w) in all the batches. The composition of the DCCSRA used in the T1, T2, and T3 batches has been given in Table 1. The concentration of DCCSRA used was 150 mg (50% w/w) in the three batches of T1 to T3. The diluent used in these batches was dicalcium phosphate dihydrate (Emcompress) at a concentration of 50 mg (16.67% w/w) in each batch. The results in Table 2 show that the flow of the DCCSRA is much superior to that of the physical blend of the two components showing that the DCCSRA is suitable for the direct compression process.

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. The trial batch blend angle of repose and tablets crushing strength and friability values have been presented in Table 4.

Table 4: Table shows evaluation of blend and tablets of Tramadol HCl compressed with DCCSRA

Parameters	Batch Code						
	T1	T2	T3	T4	T5	T6	T7
Angle of repose (°)	24	26	29	30	28	27	25
Crushing strength (N ± SD)	107±5	94±6	83±4	82±3	83±5	83±4	81±6
Friability (%)	0.07	0.11	0.14	0.13	0.10	0.12	0.12

The *in-vitro* dissolution profile in Figure 1 shows that the dissolution release decreases with increase in the concentration of glyceryl behenate in the DCCSRA. The dissolution release from formulation of Tramadol HCl prepared with DCCSRA of different ratio was in the order of 1:1 > 1:2 > 1:3. The release at each time point was highest with excipient of ratio 1:1 and lowest with ratio of 1:3. Refer to the dissolution release values of trials T1, T2 and T3 in Table 5.

Table 5 : Table shows drug release of Tramadol HCl from trial formulations T1 to T4

Time in Hours	% Mean Drug Release In 0.1N Hydrochloric acid			
	T1	T2	T3	T4
1	35	31	27	30
2	47	42	36	41
4	58	54	46	54
6	72	64	57	65
8	85	79	71	77
10	91	88	81	86
12	99	95	89	90

Effect of lactose and dicalcium phosphate

The batch T3 & T4 were formulated using the DCCSRA-Composition-III [Povidone: Glyceryl behenate: 1:3]. In batch T3 dicalcium phosphate (Emcompress) was used as diluent and in batch T4 lactose (Flowlac 100) was used as diluent. The dissolution release results of batch T3 and T4 have been shown in Figure 1 and Table 5.

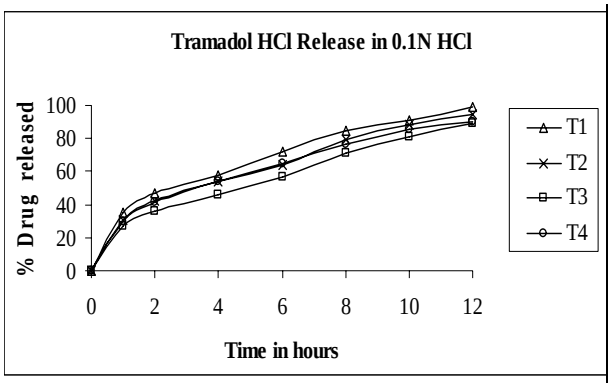

Fig.1: It shows in vitro dissolution release profile of batches T1 to T4 in 0.1N hydrochloric acid

Evaluation of dissolution profile of reference product [Zydol SR 100 mg tablet] and trial formulations

To match the dissolution profile of trial formulation with that of the reference product, the trial batches T5 to T7 were formulated by varying the concentration of co-processed multifunction sustained release agent. The DCCSRA of composition-III [povidone: glyceryl behenate (1:3)] was used for these trials. The tablet weight was kept constant at 300 mg and the difference in the concentration of DCCSRA was adjusted with dicalcium phosphate [Emcompress]. The dissolution release of batches T5 to T7 were checked in the dissolution media of three different pH values.

The *in-vitro* dissolution profile results of Zydol SR 100 mg tablet [reference product] and trial batches T5 to T7 have been presented in the Figures 2 to 4 and the dissolution release values have been tabulated in Table 6.

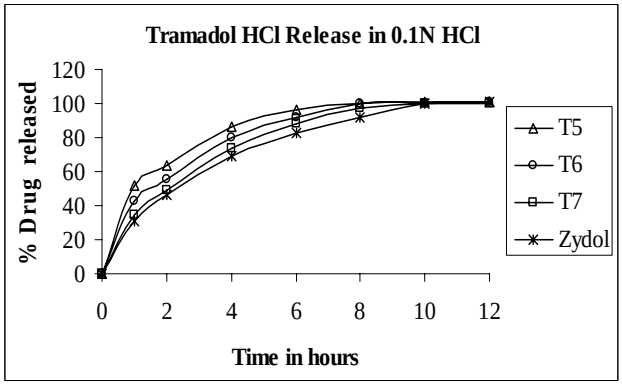

Fig.2: It shows in vitro dissolution release profile of Zydol SR 100 mg tablet and trial batches T5 to T7 in 0.1N Hydrochloric acid

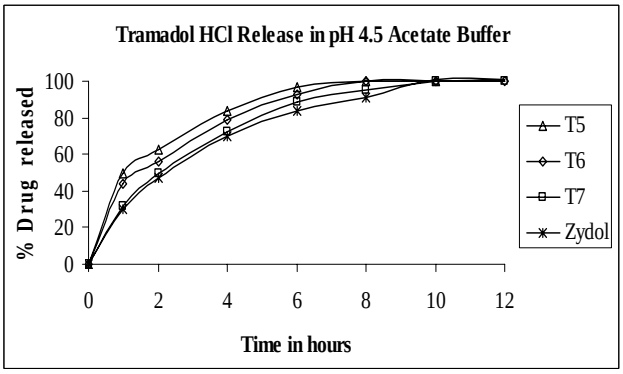

Fig.3: It shows in vitro dissolution release profile of Zydol SR 100 mg tablet and trial batches T5 to T7 in pH 4.5 Acetate buffer

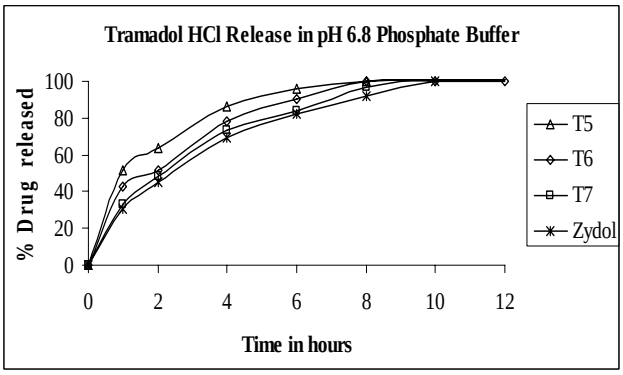

Fig.4: It shows in vitro dissolution release profile of Zydol SR 100 mg tablet and trial batches T5 to T7 in pH 6.8 Phosphate buffer

Table 6: Table shows dissolution release values of trials T5, T6, T7 and reference product Zydol SR 100 mg tablet in different dissolution media

Time in Hours	% Mean Drug Release											
	0.1N Hydrochloric acid				pH 4.5 Acetate Buffer				pH 6.8 Phosphate Buffer			
	T5	T6	T7	Zydol	T5	T6	T7	Zydol	T5	T6	T7	Zydol
1	52	43	35	31	50	44	32	30	52	43	33	31
2	64	55	49	46	63	56	50	47	64	52	48	45
4	86	80	74	69	84	79	72	70	86	78	73	69
6	96	92	88	83	97	93	89	84	96	90	84	82
8	100	100	97	92	100	100	95	91	100	100	97	92
10	101	100	100	100	100	100	100	101	101	100	101	100
12	101	101	100	101	101	100	100	101	101	100	101	101

DISCUSSION

In the present study the DCCSRAs were prepared and the feasibility of using the co-processed agent as multifunction agent in a sustained release formulation was evaluated by comparing the *in-vitro* dissolution release of the trial formulations containing Tramadol HCl with that of a reference product [Zydol SR 100 mg 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 DCCSRAs of povidone K 25 and glyceryl behenate were 23°, 25° and 28° respectively [Tables 1 and 2]. These angle of repose values show that the DCCSRAs have better flow than the physical blend of povidone and glyceryl behenate.

The angle of repose values of the 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 batch T4 was formulated with lactose (Flowlac 100) which is a soluble diluent and the batch T3 was formulated with dicalcium phosphate (Emcompress) which is an insoluble diluent. The *in-vitro* dissolution release of T4 batch was higher at all the time points when compared with T3 batch [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 7] show that the dissolution release pattern of the trial batches T6 and T7 were similar to that of reference product [Zydol SR 100 mg tablet]. Between T6 and T7, the release pattern of T7 was closer to the release pattern of the reference product [Zydol SR 100 mg tablet][10].

The stability data of the trial formulations shown in Table 8 indicate that the trial product has a satisfactory stability of up to 6 months in 40 ± 2° C and 75 ± 5% RH and at 30 ± 2° C and 65 ± 5% RH. The details of analytical method followed for assay, dissolution and related substances test of the trial product has been presented in Table 9.

Table 7: Table shows results of difference factor (f1) and similarity factor (f2*)*

Dissolution Medium	f1 Value			f2 Value		
	T5	T6	T7	T5	T6	T7
0.1N Hydrochloric acid	14.94	9.39	4.41	43.32	53.70	70.29
pH 4.5 Acetate buffer	13.93	9.92	3.44	44.99	53.04	75.48
pH 6.8 Phosphate buffer	15.38	8.65	3.27	42.80	55.81	75.64

Table 8: Table shows stability data for the trial formulation of Tramadol HCl sustained release tablets [Trial T7]

Duration & Condition	Assay Results (in %)	Dissolution release in 0.1N HCl (Mean Drug Release in %)							Related Substances (in %)		
		1st Hour	2nd Hour	4th Hour	6th Hour	8th Hour	f1 Value [0 -15]	f2 Value [> 50]	Tramadol Impurity A [NMT 0.2%]	Unknown Impurity [NMT 0.1%]	Total Impurities [NMT 0.4%]
Initial	100.2	35	49	74	88	97	6.85	66.94	0.072	0.045	0.117
40°C/ 75% RH											
1 Month	99.9	33	48	73	86	96	4.67	74.16	0.073	0.046	0.119
3 Months	99.7	34	48	74	86	96	5.30	71.66	0.074	0.046	0.120
6 Months	99.3	34	49	74	87	97	6.23	68.74	0.076	0.047	0.123
30°C/ 65% RH											
1 Month	99.9	35	49	75	87	96	6.57	67.69	0.073	0.045	0.118
3 Months	99.8	34	48	73	88	97	5.92	69.37	0.073	0.045	0.118
6 Months	99.7	35	48	74	89	97	6.85	66.34	0.073	0.046	0.119

Table 9: Table shows analytical parameters followed for stability study of trial formulation T 7

Tests	Stationary Phase	Mobile Phase	Detection wavelength	Flow rate
Assay	C-18, 250 x 4.6 mm, 5 µ (Waters- Symmetry)	1 : 30 : 69 v/v/v [Trifluoroacetic acid: Acetonitrile: Water]	271 nm	1.0 mL/min
Dissolution	C-8, 250 x 4.6 mm, 5 µ (Waters-Symmetry)	705 : 295 v/v [0.2% v/v of Trifluoroacetic acid in water: Acetonitrile]	271 nm	1.0 mL/min
Related Substances	C-18, 250 x 4.6 mm, 5 µ (Waters-Symmetry)	1 : 30 : 69 v/v/v [Trifluoroacetic acid: Acetonitrile: Water]	271 nm	1.0 mL/min

CONCLUSION

In the trial formulations using direct compression, the Tramadol HCl was directly compressed using DCCSRA and dicalcium phosphate (Emcompress). 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 trial batches T6 and T7 show that the dissolution release pattern of these batches were comparable to that of reference product [Zydol SR 100 mg tablet].

The above facts suggest that the DCCSRA which has been prepared and evaluated in this study may be used as a multifunction excipient in the sustained release formulation of Tramadol HCl tablets.

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