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Formulation taste masked orodispersible tablet of Pregabalin

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Abstract

In the present work, orodispersible tablets of Pregabalin were designed by preparing tasteless complexes of Pregabalin with weak cation ion exchange resins (KYRON T 134). The ion exchange complexes were prepared by the batch process using activated Kyron T 134 with a drug: resin ratios 1:1, 1:2, 1:3 and 1:4 (% w/w). IR analysis, assay content and decomplexation studies confirmed complex formation. It was found that maximum complexation of drug with resin was noted between pH range 5.5-7, while activation of ion exchange resin does not affects the percent drug loading. Drug release from drug: resin complex in salivary pH was insufficient to impart bitter taste. A study on super-disintegrants along with directly compressible diluents is studied and its effect on disintegration time and enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity and in vitro dispersion time. Based on in vitro disintegration time (approximately 30 s), formulations were tested for in vitro drug release pattern (in 0.06 N HCl),

Keywords: Orodispersible Tablet;Pregabalin; Ion exchange Resin; Kyron T 134.

Introduction

Many patients find difficulty to swallow tablets and hard gelatin capsules, consequently they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy [1]. For this reason the development of an orally disintegrating or rapidly disintegrating tablet (RDT) have recently interested not only the pharmaceutical industry, but also academia [2] Actually RDT tablets are preferred by an increasing number of patients especially children and elderly, but also adult consumers who like to have their medication readily available at any time. Patients appreciate the convenience and the discreteness of these products which can be taken without water and which guaranty a rapid onset of action [3]. The European Pharmacopoeia adopted the term orodispersible tablet as a tablet to be placed in the mouth where it disperses rapidly before swallowing and which disintegrates in less than 3 min. There was no specification concerning neither the hardness nor the friability of this kind of tablets. That is why we find certain RDT in the market that disintegrate in less than 1 min or maybe 30 s. but are brittle and require specified peel able blister packaging and thus higher costs [4].Commercially available RDT are prepared by various techniques [5], mainly lyophilisation [6,7], molding and direct compression [8]. The lyophilisation and molding techniques produce RDT which disintegrate within about 30 s, but that have low physical resistance and high friability. On the other hand, tablets obtained by direct compression are less friable but disintegrate in a longer time [9].

Attempts were made in order to decrease the disintegration time of RDT that have sufficient hardness prepared by direct compression [10]. Bi *et al.* [11] and Watanabe *et al.* [12] used microcrystalline cellulose (MCC) and low-substituted hydroxypropyl cellulose (L-HPC) as disintegrants to prepare RDT by direct compression. According to the authors the ratios of these two disintegrants MCC/L-HPC in the range of 8:2–9:1 resulted in tablets with the shortest disintegration times. While Bi *et al.* [11] used a wet compression method where wet granules of -lactose monohydrate were compressed and then the formed wet tablets were dried at 60 ◦C and kept in a desiccator for 12 h at room temperature. Formed RDT showed a disintegration time of less than 30 s and a hardness of 0.5MPa.Thus the first part of our study consisted of the preparation of taste masked complex of the active principal and ionexchange resin and the evaluation of the complex using XRD. Thereafter, the second part of the study encompassed the preparation of tablets to evaluate the potential of compressing prepared complex using different excipient. The potential of addition of croscarmellose sodium, sodium starch glucolate and crosspovidone [12] as a disintegrating agent was also evaluated. Finally, the technological characteristics of the prepared tablets were evaluated in order to find the formula with the least time of disintegration and friability and eventually the best hardness.

Pregabalin is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures with or without secondary generalization in adults [13]. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a

glass of water; hence it is beneficial to administer such drugs as ODTs. Pregabalin is an intensely bitter drug; hence, if it is incorporated directly into an ODT the main objective behind formulation of such a dosage form will definitely get futile.

Ion exchange resins have been used as drug carriers in pharmaceutical dosage forms for taste masking [14]. Ion exchange resins are cross linked water-insoluble polymers carrying ionizable functional groups. Drugs can be loaded into an ion exchange resin by an exchanging reaction, and hence a drug–resin complex is formed [15]. Drug is released from the resinate by exchanging with ions in the gastro-intestinal fluid, followed by drug diffusion [16]. There are literature reports on the interaction of amine drugs with polycarboxylic acid ion- exchanged resin[14, 17] that indicated these resins might be very useful in the taste masking. One study indicated that saliva, with an average pH of 6.7 and a cation concentration of 40 meq/L, would only elute a few percent of drug from polycarboxylic acid resin adsorbate [18]. Thus in the present study an attempt has been made to mask the taste of Pregabalin and to formulate ODTs with good mouth feel so as to prepare a "patient-friendly dosage form."

Material and Methods

Materials

Pregabalin was a gift from Glenmark pharmaceuticals (Mumbai). KYRON T 134 was a gift from Corel Pharma-Chem. Ahmedabad, India. Sodium starch glycolate, Croscarmellose sodium, Crospovidone Mannitol and silicified microcrystalline cellulose were provided as gift samples by Signet chem.. and flavor of Firmenich were provided by Manish global. All other chemicals used in the study were of analytical grade.

Method

Purification of ion exchange resin KYRON T 134 was washed with distilled water. The wet resin was activated by 0.1 M HCl 300 ml followed by washing with distilled water and was dried overnight in hot air oven at 50 C and was stored in an air tight container [19].

Preparation of Pregabalin resinate

Pregabalin resinate was prepared using a batch process. For preliminary study, we optimized the ratio of resin to drug at 1:3. Drug (5.0 g) Resin (15.0 g) was placed in an glass beaker and then 380 ml of distilled water was added. The mixture was stirred in the water bath at 37 C. The supernatant was collected and assayed at a wavelength of 210 nm (using HPLC) to determine the drug-loading equilibrium time. Then, the Pregabalin resinates were separated from the filtrates by filtration, washed several times with distilled water, dried overnight at 50 C and kept in air tight container [19,22].

Characteristics of Pregabalin resinates

Pregabalin content

Pregabalin resinate (equivalent to 300 mg of Pregabalin) was placed in a beaker to which 0.06 N HCl (50 ml) was added for eluting Pregabalin from the resinate. The eluate was decanted and replaced with the same volume of fresh eluent. The volume of eluate was measured and assayed for the content of Pregabalin at a wavelength of 210 nm (using HPLC). The elution process was stopped when the absorbance of the last eluate was lower than 0.01. The sum of the content of Pregabalin in each eluate was equal to the total content of Pregabalin in resinate. (Table 1)

In vitro taste Evaluation

In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. Solid drug: resin complex equivalent to 100 mg of drug was subjected to release rate study. Weighed quantity added to 10 ml phosphate buffer pH 6.8 Aliquot was withdrawn after 2 min. The sample was filtered through 0.45µm milipore filter. The absorbance was measured at a wavelength of 210 nm (using HPLC) (Table 1).

Table 1. Drug content and *in vitro* taste evaluation of drug resin complex in simulated salivary fluid

Ratio of drug :resin complex	1: 2	1: 3	1: 4
Assay of drug resin complex	90.12	99.8	99.9
% Drug dissolved in SSF after Time 2min*	10. 0±0.314	1.110±0.112	0.764±0.17
Assay of pure drug	99.9		

Molecular Properties

Molecular properties on complexation were studied by x-ray powder diffraction (XRPD). The X-ray powder diffractograms of the Drug: KYRON T 134 (1:4), Pregabalin, and KYRON T 134 were recorded. using a Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Saint Jurie, Clubac, Canada) with monocrotized Cu K radiation (1.314 A0), at a speed of 2θ min–1 from 10- to 60-(2θ) under the voltage and current of 40 Kv and 30 Kv respectively (Figure 1,2 & 3).

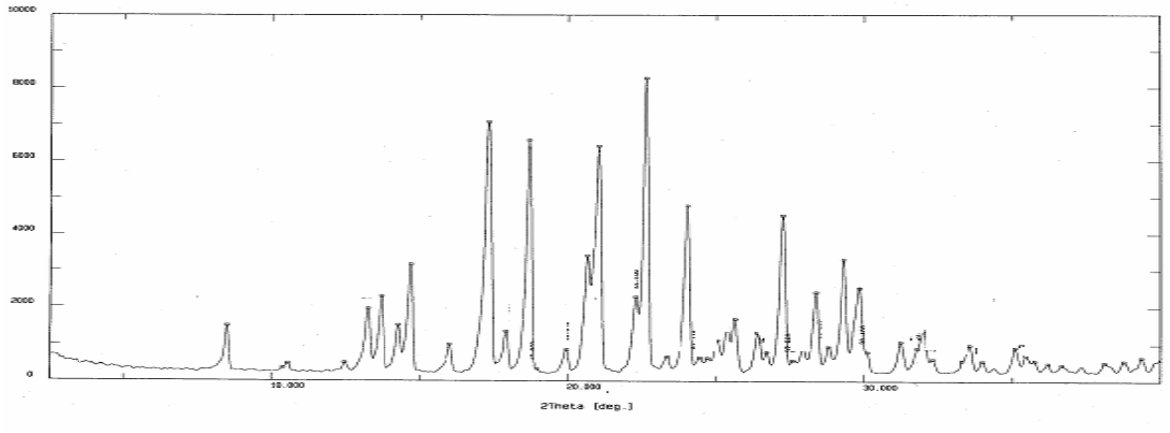

Figure 1. X-ray diffraction pattern of pregabalin

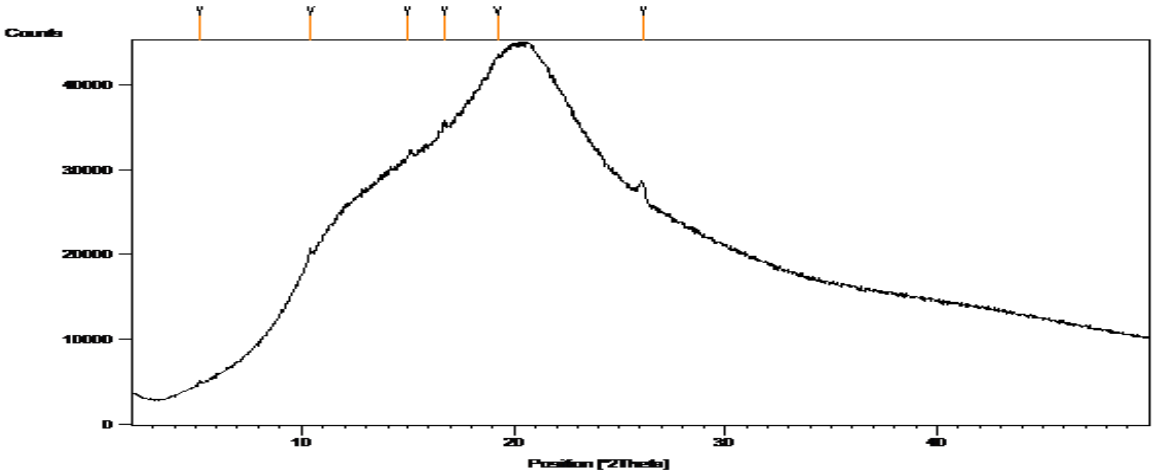

Figure 2. X-ray diffraction pattern of kyron T 134

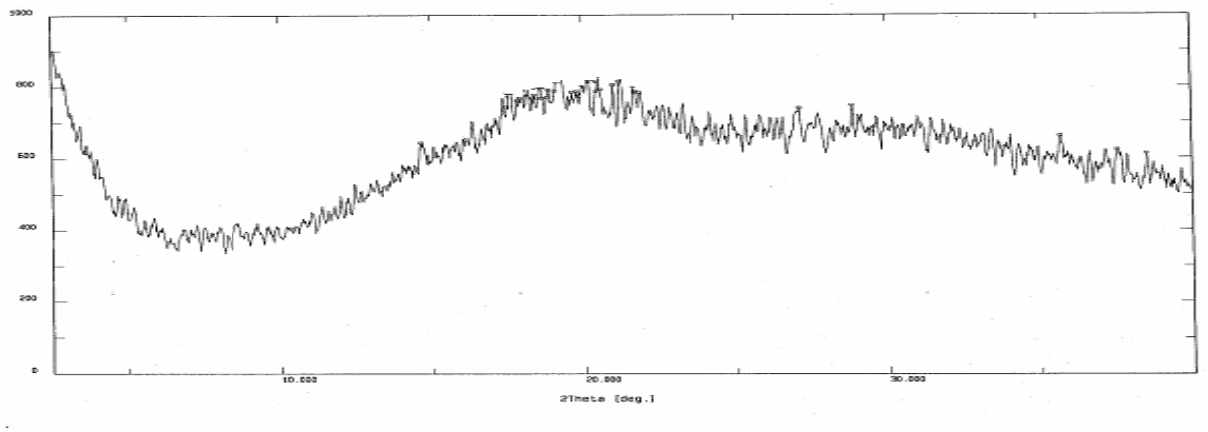

Figure 3. X-ray diffraction pattern of drug: resin complex

Selection of Superdisintegrant and Formulation of ODTs

Before formulation of tablets, the best superdisintegrant among Sodium starch glycolate, Croscarmellose sodium and Crospovidone was screened out (Table 2). The best superdisintegrant screened was used for the final formulation of tablets (Table 3). Tablets were prepared in various batches containing a blend of mannitol, microcrystalline cellulose and sorbitol (directly compressible) diluents and superdisintegrant in various concentrations (Table 4). Tablets were prepared by direct compression using 8.0 mm round for 25 mg and 13.0 mm for 100 mg, standard concave beveled edge punch.

Table 2. Selection of superdisintegrant

Sr no	Batch	Disintegrant	%/ tab	Disintegration Time (Sec)*
1	D1	--		150.0±5.00
2	D2	Cros Carmellose sodium	3	70.36±1.04
3	D3		5	55.95±2.62
4	D4		7	50.26±2.53
5	D5	Sodium Starch Glycollate	3	78.16±2.04
6	D6		5	59.95±2.57
7	D7		7	55.7±3.79
8	D8	Cros Povidone	3	50.05±1.22
9	D9		5	35.30±1.48
10	D10		7	30.73±2.45

Table 3. Optimization of disintegration

Sr no	Batch	Disintegrant	Quantity mg / tab	Disintegration Time (Sec)*
1	D8	Cros Povidone	4	50.05±1.22
2	D9		6	35.30±1.48
3	D10		8	31.30±2.45
4	D11		5	43.30±1.67
5	D12		7	31.40±1.82
6	D13		10	38.20±3.78

Table 4. Formulation composition for an ODT

Sr no	Ingredient / tablet	Formulation							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Drug resin complex	400.0	400.0	400.0	400.0	400.0	400.0	400.0	400.0
2	Mannitol SD 200	184.6	-	-	27.0	-	10.0	10.0	110.0
3	Sorbitol	-	184.6	-	110.0	27.0	117.0	127.0	27.0
4	MCC (Avicel 112)	-	-	184.6	-	110.0	10.0	-	-
5	Starch 1500	-	-	-	47.6	47.6	47.6	47.6	47.6
6	PVP K-30	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
7	Crosspovidone	49.0	49.0	49.0	49.0	49.0	49.0	49.0	49.0
8	Sucralose	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
9	Mint	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
10	Colloidal silicon dioxide	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2
11	Magnesium stearate	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2

*- Drug resin complex (DRC) equivalent to 100 mg of Pregabalin.

Physical Properties of the Tablet Blend

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined (Table 5). Bulk density was determined by the USP method I; tapped density was determined by USP method II. Percent compressibility was calculated using Equations 1. Percent compressibility = {(D t D b) / D t } 100 .....(1)
Where, Dt and Db are tapped and bulk densities [20].

Table 5. Physical properties of tablet blend

Batch No	Bulk density (g/mL)	Tapped density (g/mL)	Angle of Repose* ( )	% Compressibility	Hausner ratio
F1	0.58	0.68	26.56±0.70	14.71	1.18
F2	0.57	0.67	25.45±0.60	14.93	1.18
F3	0.48	0.64	27.13±0.78	25.00	1.33
F4	0.56	0.65	26.5±0.67	13.85	1.16
F5	0.52	0.66	26.45±0.85	21.21	1.27
F6	0.54	0.65	25.25±0.54	16.92	1.20
F7	0.56	0.66	27.61±0.63	15.15	1.18
F8	0.56	0.65	26.21±0.43	13.85	1.16

Evaluation of Tablet

The prepared orodispersible tablets were evaluated for hardness, weight variation, thickness, friability and drug content (Table 6) [21]. Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tabmachine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier calliper. Weight variation test was performed according to the official method as per USP.

In Vitro Disintegration Time

In vitro disintegration time for RDTs was determined using USP and disintegration of tablet in a beaker containing 50 ml of SSF. The volume of the media will give a discriminatory nature to the disintegration time.

Table 6. Physical properties of tablet

Batch No.	Friability	Hardness (Kg/cm2)	Thickness	% Weight variation	Disintegration time (Sec)
F1	0.72 ± 0.19	10.13±0.24	5.40 ± 0.05	700.20± 1.70	55.0± 2.2
F2	0.65 ± 0.2	10.30±0.24	5.40 ± 0.02	700.50± 1.80	52.0± 3.0
F3	0.89 ± 0.14	7.50±0.24	5.39 ± 0.04	700.00± 1.20	30.0± 4.0
F4	0.70 ± 0.59	10.50±0.20	5.48 ± 0.06	700.70± 1.35	35.0± 4.0
F5	0.66 ± 0.32	7.50±0.30	5.40 ± 0.03	700.70± 1.40	32.0± 1.0
F6	0.59 ± 0.24	10.00±0.32	5.39 ± 0.07	700.20± 1.80	35.0± 4.0
F7	0.68 ± 0.18	10.70±0.25	5.39 ± 0.03	700.15± 1.50	40.0± 4.0
F8	0.56 ± 0.29	11.20±0.40	5.38 ± 0.02	700.10± 1.50	38.0± 2.0

In-vitro Dissolution studies

The *in-vitro* dissolution studies were carried out using USP apparatus type II (paddle) at 50 rpm.
The dissolution medium used was 0.06 N HCl (900 ml) maintained at 37 ± 0.5 C. Aliquots of dissolution media were withdrawn at different intervals and content of Pregabalin was measured at a wavelength of 210 nm (using HPLC). The dissolution experiments were conducted in triplicate. Results were shown in figure 4, 5 and 6.

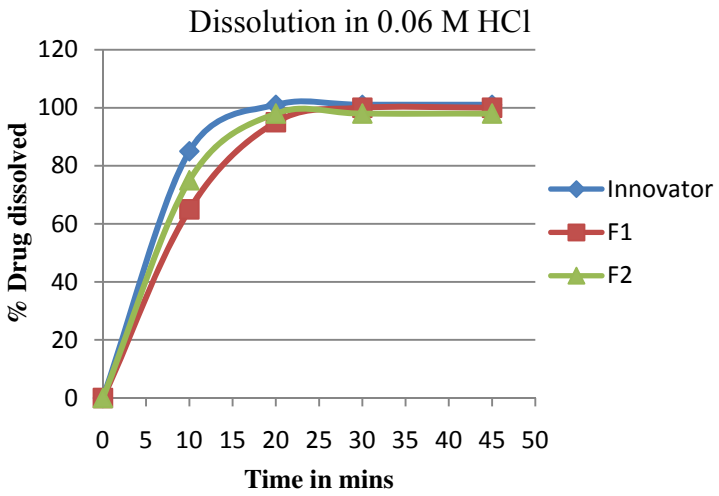

Figure 4. *In-vitro* release profile of capsule of marketed product and batches F1 & F2

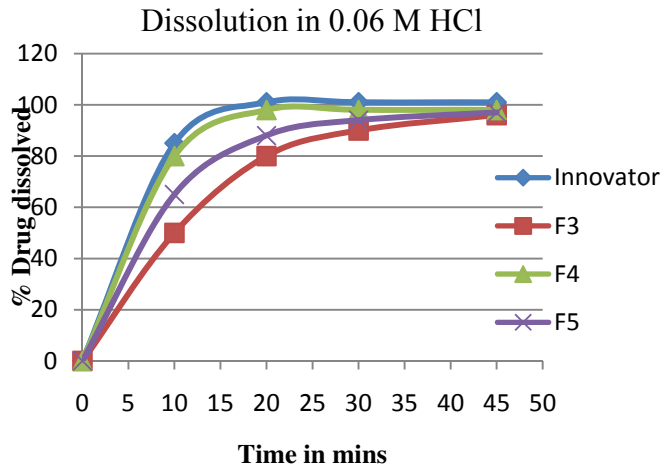

Figure 5. *In-vitro* release profile of capsule of marketed product and batches F3 TO F5

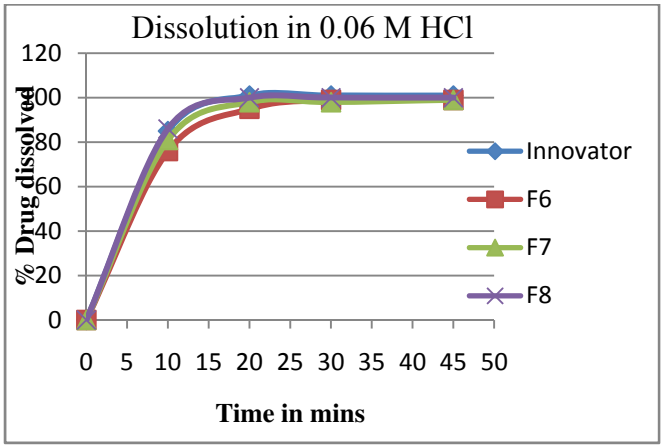

Figure 6. *In-vitro* release profile of capsule of marketed product and batches F6 TO F8

Comparison of Optimized Formulation with Marketed Capsule

In vitro Dissolution studies for optimized formulation and Marketed Capsule were also carried out (Figure 6).

Results and Discussion

Characterization of DRCs (Drug resin complex)

Percentage drug loading in DRCs was found from 96.12 to 99.9. No drug release was observed in SSF from complexes with the drug-polymer ratio of 1:3 and ratios with lesser drug, therefore, the ratio 1:3 was considered the optimal DRC with complete masking of bitter taste for further studies. The x-ray diffractogram of Pregabalin confirms its crystalline nature, as evidenced from the number of sharp and intense peaks (Figure 1). The diffractogram of resin (KYRON T 134) showed diffused peaks, indicating its amorphous nature (Figure 2). However, the diffraction pattern of DRC (1:3) represents complete disappearance of crystalline peaks of drug (Figure 3). These finding suggest the formation of new solid phase with a lower degree of crystallinity due to complexation .

Selection of the Superdisintegrant

The formulation of orordispersible tablet was made by using Pregabalin- resin complex. Batches D1 to D10 were prepared by direct compression to select the disintegrant, from the results shown in Table 2, it can be concluded that the tablets containing crospovidone (D8 – D10) exhibit quick disintegration time and followed by croscarmellose sodium and sodium starch glycolate. The probable reason for delayed disintegration time of the tablets might be slow water uptake or more felling tendency of croscarmellose sodium and sodium starch glycolate than crospovidone or gel formation at higher percentage. Hence crospovidone was selected as a disintegrant for the further studies.

From the results shown in Table 3 is obvious that the maximum concentration of crospovidone might be less than 10%. Batches D8 - D13, were prepared to optimize the optimum concentration of crospovidone in order to obtained rapid disintegration at minimum concentration. The composition and results of batches are shown in Table 4. Batch D10 had shown more decrease in disintegration time but not more efficient then D12, on further increasing the concentration as in batch D13 there was increase in disintegration time for this reason batch S12 was selected so as to avoid any delay in disintegration time due to increase in disintegrant. Sometimes increase in disintegrant concentration decreases disintegration time, such behaviour of superdisintegrant may be due to the blockade of capillary pores which prevents the entry of fluid into the tablet.

Physical Properties of the Tablet Blend

The tablet blend of all the batches was evaluated for different derived properties viz- angle of repose (between 25 to 27), bulk density (between 0.48 to 0.57 gm/cm3), Compressibility index (between 13 to 25). The results angle of repose and compressibility indicated that the flowability of blend is significantly good. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 7.50±0.24 to 11.20±0.40 Kg/cm2 in all the formulations. The hardness of all tablets was kept within the above mentioned range to compare the disintegration time between the formulations prepared using different disintegrants and their varying concentrations. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was between 5.38±0.02 –5.48 ± 0.06 mm showing fairly uniform tabletting. The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of Orodispersible tablet. The values were found to be in the range of 32.0± 1.0 to 55.70 ± 2.2 sec. The time intensity study for taste in human volunteers of both the DRC and ODT revealed considerable masking of the bitter taste of Pregabalin with degree of bitterness below the threshold value (0.5) ultimately reaching to 0 within 15 minutes. Sensory evaluation of the optimized tablet proved good palatability.

Drug Release from ODT

All the tablets prepared were subjected for release profile. The tablets prepared from crospovidone i.e. F1 to F8 showed a drug release upto 100% (Figure 4, Figure 5 and Figure 6) (Table 7a and 7b). Among eight batches, batch F8 which contain sorbitol and Mannitol along with crospovidone was selected as optimized batch because of its lowest disintegration time and highest drug release. The drug release of the marketed product and F8 formulation was found to be 100 ± 1.52 and 100.0 ± 1.68 at the end of 20 minutes. From the above observations, it may be concluded that optimized

formulation is better or as good as an marketed conventional capsule in release rate of drug with taste masked characteristic.

Conclusion

The study conclusively demonstrated complete taste masking of Pregabalin, rapid disintegration and dissolution of ODT. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of Pregabalin in a more palatable form without water during emesis. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non co-operative patients, can be successfully formulated using this technology.

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