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Formulation development and process comparison of different compressed oral disintegrating tablets

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ABSTRACT

The aim of the present investigation was to develop simple oral disintegrating tablets (ODT) for industrial purpose with different category of drugs like granisetron hydrochloride, memantine hydrochloride, amlodipine besylate, desloratadine, zaleplon and risperidone using different formulation and process. Granisetron hydrochloride (GRN), memantine hydrochloride (MEM), amlodipine besylate (AML) and zaleplon (ZAL) drugs are low bitter and low dose drugs. ODT of these drugs were prepared to using direct compression tablets techniques with simple taste and flavors enhancers. ODT of desloratadine (DES) and risperidone (RIS) were prepared using wet granulation tablets technique with different taste masking agents, taste and flavor enhancers, because these two drugs are highly bitter with low dose drugs. Simple taste and flavor enhancers were not sufficient to mask bitterness of these drugs. Amberlite was used as a taste masking agent, Mannitol was used as a diluents, Acesulfame potassium, aspartame and peppermint was used as a flavoring agent. The results revealed that the tablets containing taste masking had a good palatability for the patients. It was concluded that all the ODT's with improved taste masking and dissolution could be prepared by simple compressed tablet technique with suitable excipients. This work helped in understanding the effect of oral disintegrating tablets formulation and processing comparison of compressed tablet technique, especially the disintegrating and taste masking agents on the drug taste masking, disintegration time and release profile. The present study demonstrated potentials for rapid disintegration in oral cavity with out water, improved taste masking and patient compliance.

Keywords: Oral disintegrating tablets (ODTs), compressed tablet technique, Granisetron hydrochloride, Memantine hydrochloride, Amlodipine besylate, Desloratadine, Zaleplon Risperidone and Amberlite IRP 64 Resin.

INTRODUCTION

Oral disintegrating tablets (ODT) are solid unit dosage forms which disintegrate or dissolve rapidly in the mouth without chewing and water. ODTs are also called as fast melt, fast disintegrating tablets. In April 2007, the FDA issued draft guidance, Guidance for Industry: Orally Disintegrating Tablets. It considers ODTs to be solid oral preparations that disintegrate rapidly in the oral cavity with an *in vivo* disintegration time of approximately 30 seconds or less, when based upon the USP disintegration test method or alternative [1].

ODT formulation containing ingredients which disintegrates rapidly, usually within matter of seconds, when placed upon the tongue, but which releases a drug (or drugs) at a time other than promptly after administration [2, 3]. The European Pharmacopeia however defines a similar term, orodispersible tablets or tablets intended to be placed in the mouth where it disperses rapidly before swallowing [4]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. ODTs are appreciated by a significant segment of population, particularly children and elderly, which have difficulty in swallowing conventional tablets or capsules [5-7].

The fundamental principle used in the development of the ODTs is to maximize its pore structure. Researchers have evaluated spray dried materials and soluble materials for development of such tablets. ODTs can be prepared by various techniques, mainly compression, lyophilization and moulding. The simplicity and cost effectiveness of the compression process have positioned this techniques as an attractive alternate to traditional granulation technologies. Usually superdisintegrants are added to a drug formulation to facilitate the disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants [8].

Granisetron is widely used antiemetic to treat nausea and vomiting following chemotherapy. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base) [9].

Memantine hydrochloride is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride. The molecular formula is $C_{12}H_{21}N$•HCl and the molecular weight is 215.76. Memantine HCl occurs as a fine white to off-white powder and is soluble in water. Memantine hydrochloride is available as tablets or as an oral solution [10].

Amlodipine besylate is chemically described as 3-Ethy l-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$. Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol [11].

Zaleplon is widely used short-term treatment of insomnia. Chemically it is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide. Its empirical formula is $C_{17}H_{15}N_5O$, and its molecular weight is 305.34. Zaleplon is rapidly and almost completely

absorbed following oral administration. Peak plasma concentrations are attained within approximately 1 hour after oral administration. Although zaleplon is well absorbed, its absolute bioavailability is approximately 30% because it undergoes significant presystemic metabolism [12].

Desloratadine is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol. It has an empirical formula: $C_{19}H_{19}ClN_2$ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*-benzo[5,6] cyclohepta [1,2-*b*]pyridine [13].

Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution [14].

The objective of the present study was to compare the formulation and process of different category of orally disintegrating tablets with compressed tablet technique and to investigate the effect of taste masking on the patient compliance and super disintegrating agent on the disintegration and release profile of the drug in the tablets.

MATERIALS AND METHODS

2.1. Materials

Granisetron hydrochloride, Memantine hydrochloride, Amlodipine besylate, Zaleplon, Desloratidine and Risperidone, Amberlite IRP 64 resin, Citric Acid, L- Hydroxypropyl cellulose 21 (L-HPC 21), Deionised water, Microcrystalline cellulose (Avicel pH 101) NF, Croscarmellose sodium NF (Ac-di-sol), Colloidal Silicon Dioxide NF (Aerosol 200), Mannitol NF (Pearlitol SD200), Crospovidone NF (Polyplasdone XL 10), Peppermint Flavor Premium 501500 TP0504, Acesulfame Potassium NF, Aspartame NF, Sodium lauryl sulphate NF (Stepanol WA100), menthol and Sodium Stearyl Fumarate NF (Pruv) were obtained as gift sample from Orchid Healthcare, Irungattikottai, Chennai and Hetero drugs limited, Hyderabad. All other chemicals and reagent were of analytical grade.

2.2. Method

2.2.1. Formulation of oral disintegrating tablets (ODT's)

The Oral disintegrating tablets of different drugs were prepared using the crospovidone and croscarmellose sodium as superdisintegrants, mannitol and microcrystalline cellulose as a diluents, Amberlite IRP 64 resin as a taste masking agent, L- Hydroxypropyl cellulose 21 used as a solubility enhancer and binder, aspartame and acesulfame potassium as a sweetening agents or taste enhancers, peppermint flavor as a flavor enhancers, menthol as a cooling agent, citric acid as a buffering agent, deionised water used as a vehicle for granulation, sodium lauryl sulphate as a solubility enhancer of the drug, colloidal silicon dioxide and sodium stearyl fumarate (Pruv) as a flow promoter. The composition of the each formulation is shown in below Table 1.

Granisetron hydrochloride (ODT1), Memantine hydrochloride (ODT2), Amlodipine besylate (ODT3) and Zaleplon (ODT4) drugs are low bitter in nature, so direct compression process was selected for ODT formulation development.

Direct compression process was selected for formulation development, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration, simple process, no critical steps and unit operations involved, cost effective and minimum time required for process. In this process, mannitol and colloidal silicon dioxide were together passed through sieve no. 40 (Blend 1). Drug, peppermint flavor, crospovidone, aspartame, acesulfame potassium and sodium lauryl sulphate (only in ODT4) were mixed and sift together through sieve no. 60 (Blend 2). The mannitol blend (Blend 1) part and drug blend (Blend 2) part were mixed with serial blending and finally passed through sieve no. 40 (ODT1 to ODT4). This final blend was compressed into tablets using flat face round 9.0mm tooling on a 16 station tablet machine and tablets were evaluated.

Desloratadine (ODT5) and Risperidone (ODT6) drugs are highly bitter in nature; direct compression process was not suitable for these ODT formulation developments. Taste masking agent was used in this formulations to mask the bitterness of the drugs, so wet granulation process were selected for these two formulations.

The Oral disintegrating tablets of risperidone and desloratadine were prepared using the Croscarmellose sodium (Ac-di-sol) and crospovidone (polyplasdone XL 10) as superdisintegrants, microcrystalline cellulose (Avicel PH 101) and mannitol as diluents, amberlite as taste masking agent, aspartame and acesulfame potassium as sweetening agents or taste enhancers, peppermint flavor and menthol as a flavor enhancers, L-Hydroxypropyl cellulose Type 21 as binder, citric acid as a buffering agent, colloidal silicon dioxide and sodium stearyl fumarate (Pruv) as flow promoter. The composition of the each batch was shown in Table 1.

For desloratadine oral disintegrating tablets, raw materials were passed through a #40mesh screen prior to mixing. Desloratadine was dispersed in purified water under stirring. The pH of the drug dispersion was adjusted to pH 6.5±0.5 with 2%w/v citric acid solution. Amberlite IRP64 was added to the pH adjusted drug dispersion and stirred for 3 hours. The desloratadine and polacriline resinate in dispersion was filtered through vacuum filter and was dried at 60^{o}C till to get LOD (at 105^{o}C) below 4-6%w/w. The dried mass was passed through #24mesh. The dried granules were blend with Mannitol, crospovidone, peppermint flavor, acesulfame potassium, aspartame and Colloidal Silicon Dioxide (Aerosol 200) in octagonal blender for sufficient time and finally lubricated with sodium stearyl fumarate. The final blend was then compressed into tablets using flat face round 9.0mm tooling on a 16 station tablet machine and tablets were evaluated.

For risperidone oral disintegrating tablets, raw materials were passed through a #40mesh screen prior to mixing. The amberlite and risperidone dispersed in deionised water under stirring for 2hour and L-Hydroxy Propyl cellulose Type 21 was added to above drug solution under stirring for 20min. Same suspension was used as a granulating fluid. Microcrystalline cellulose (Avicel PH 101), Croscarmellose sodium (Ac-di-sol) and L-Hydroxypropyl cellulose Type 21 loaded in rapid mixer granulator and dry blend mixed for 10 min and granulated with above mentioned

drug suspension. The wet mass was dried and passed through sieve no. 24. The dried granules were blend with Mannitol, crospovidone, peppermint flavor, acesulfame potassium, aspartame, L-Hydroxy Propyl cellulose Type 21, Menthol and Colloidal Silicon Dioxide NF (Aerosol 200) in octagonal blender for sufficient time and finally lubricated with sodium stearyl fumarate. The final blend was then compressed into tablets using flat face round 9.0mm tooling on a 16 station tablet machine and tablets were evaluated.

Table 1: Composition and comparison of different formulations of oral disintegrating tablets

Ingredients	ODT1	ODT2	ODT3	ODT4	ODT5	ODT6
Drug	2.0	10.0	10.0	10.0	5.0	2.0
Amberlite IRP 64 resin	--	--	--	--	15.0	6.0
Citric Acid	--	--	--	--	1.8	--
L-HPC 21	--	--	--	--	--	1.0
Deionised water	--	--	--	--	q.s	q.s
MCC (Avicel 101)	--	--	--	--	--	40.0
Ac-di-sol	--	--	--	--	--	6.0
L-HPC 21	--	--	--	--	--	2.0
Colloidal Silicon Dioxide (Aerosol 200)	8.8	8.8	8.8	8.3	2.0	2.0
Mannitol NF (Pearlitol SD200)	148.8	159.3	159.3	140.4	148.2	115.1
L-HPC 21	--	--	--	--	--	4.0
Crospovidone NF (Polyplasdone XL 10)	16.0	16.5	16.5	16.0	10.0	8.0
Peppermint Flavor Premium 501500 TP0504	3.8	3.9	3.9	3.8	2.0	2.0
Acesulfame Potassium	6.8	6.6	6.6	7.0	6.0	5.0
Aspartame	3.8	3.9	3.9	4.0	4.0	0.7
Menthol	--	--	--	--	--	0.2
Sodium lauryl sulphate (Stephanol WA 100)	--	--	--	0.5	--	--
Sodium Stearyl Fumarate (Pruv)	10.0	11.0	11.0	10.0	6.0	6.0
Total	200.0	220.0	220.0	200.0	200.0	200.0

2.2.2. Evaluation of formulated tablets

2.2.2.1. Hardness

The crushing strength of the tablets was measured using an Erweka hardness tester. Twenty tablets from each formulation batch were tested randomly and the average reading noted.

2.2.2.2. Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±5%

2.2.2.3. Thickness

The thickness of the tablets was measured using Vernier Caliper (Mitu-tyo). Twenty tablets from each formulation batch were tested randomly and the average reading noted.

2.2.2.4. Friability

6.5g of equivalent weight tablets were weighed and placed in a friabilator (Electrolab ET-2). Preweighed tablets were roated at 25 rpm for 100 rotations. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

2.2.2.5. Disintegrating time

In vitro disintegration time was measured by using disintegration tester (Electrolab ED-2L) and tablet dropping in a 1000ml beaker containing 900ml of purified water which maintained at 37±0.5°C.

Table 2

Sr. No	Product name	Apparatus	Speed	Medium	Volume (mL)	Sampling points
1	Granisetron HCl tablets	II (Paddle)	50	Phosphate buffer, pH 6.5	500	10, 20, 30, 45 and 60
2	Memantine HCL tablets	I (Basket)	100	0.1 N HCl with NaCl (12 g NaCl in 6 L water adjust pH to 1.2 with HCl)	900	10, 20, 30 and 45
3	Amlodipine Besylate ODT tablets	II (Paddle)	50	0.01 M HCl	500	5, 10, 15 and 20
4	Zaleplon capsules	II (Paddle)	75	Deionised water	900	5, 10, 20, and 30
5	Desloratadine ODT tablets	II (Paddle)	50	0.1 N HCl	900	3, 6, 10, 15
6	Risperidone ODT tablets	II (Paddle)	50	0.1 N HCl	500	5, 10, 15

2.2.2.6. Dispersion time
In vitro dispersion time was measured by dropping a tablet in a 10 ml measuring cylinder containing 6 ml of buffer solution simulating saliva fluid (pH 6.8)

2.2.2.7. Dissolution
Based on the OGD guidelines, recommended dissolution methods were taken for dissolution study of ODT formulations represented as Table-2.

2.2.2.8. Taste evaluation study
The objective of this study is to conduct and evaluate the palatability of different formulations of oral disintegrating tablets. Granisetron hydrochloride, memantine hydrochloride, amlodipine besylate and zaleplon ODT were a new developments; reference product is not available in market for these products for comparison of the taste evaluation. Total eight formulations were selected for taste evaluation study, six test formulations, one positive control (Placebo for drug) and one is negative control (Placebo for Taste enhancers like aspartame and acesulfame potassium and peppermint flavor). All formulations (formulation code) were randomized. Each randomization order was assigned with sequence code. For this study we selected ten healthy human male volunteers and were assigned volunteer code.

All the ten volunteers were evaluated all eight formulations as per the randomization order. Each of the eight formulations were transferred to HDPE bottles and labeled only with formulation code. Palatability evaluation feedback format prepared and submitted to each individual volunteer and were provided with instructions before starting study. One tablet of each formulation was given to volunteer for palatability study evaluation. The time interval between evaluations of each test formulation in the same volunteer was 30min, at after evaluated each formulation, one half of a bread slice was given to each volunteer followed by half glass of water and coca powder for neutralizing the taste buds. After completion of the study, data was compiled and evaluated the formulations and allotted the rank for all formulation, based on the average value of the each formulation.

RESULT AND DISSCUSSION

Water insoluble diluents such as starch and dicalcium phosphate were omitted from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents considered its advantages in terms of easy availability and negative heat of dissolution. Table 3 shows that all the formulated tablets exhibited low weight variation. The batches ODT1, ODT2, ODT3 and ODT4 were prepared using polyplasdone XL 10 as a disintegrating agent, it is responsible for faster water uptake, hence it facilitates wicking action and bringing about faster disintegration. Acesulfame potassium, aspartame and peppermint flavor were used as a taste and flavor enhancers in all formulations. In wet granulation process (ODT5 & ODT6), addition of amberlite as a taste masking agent, L HPC 21 (ODT6) as a binder and citric acid (ODT5) as a buffering agent or neutralizing agent had no pronounced effect on flow. Menthol was used as a cooling or flavor agent in ODT6, because risperidone is a highly bitter drugs. The disintegration time and *in vitro* dispersion time of the tablets were slightly increased in tablets containing wet granulation, because less porous nature of the blend (Table 1). Desloratadine is sparingly soluble in purified water. For better interaction with the ion exchange resin, it was sought that the drug

be available in solubilized (cationic) form for interaction with ion exchange resin which is a weakly acidic resin with H^+ ion as an exchangeable cation. Hence citric acid was used to adjust pH to soluble the API (ODT5).

The drug content of all the formulations was found to be between 99.6 – 101.2% which was within the acceptable limits as per USP XXVII.

Tablets with direct compression (ODT1, ODT2, ODT3 and ODT4) were shown faster disintegration and more porability due to increased porosity. Tablets with wet granulation (ODT5 and ODT6) were shown slower disintegration than direct compression tablets, because less porous nature of the blend, but the entire tablets disintegration shown less than 30seconds as per USP.

Table 3. Evaluation of physicochemical parameters of oral disintegrating tablets

Formulation	Weight variation (mg)	Hardness (Kp)	Friability (%)	Drug content (%)	In vitro dispersion time (Sec)	Disintegration time (Sec)
ODT1	200±2	4.0±1.0	0.421	100±2	17	12±2
ODT2	220±2	4.5±1.0	0.326	100±2	17	11±2
ODT3	220±2	4.5±1.0	0.374	100±2	18	11±2
ODT4	200±2	4.4±1.5	0.416	100±2	18	12±2
ODT5	200±2	3.7±0.3	0.436	100±1	26	10±3
ODT6	200±2	3.0±0.5	0.52	100±1	29-33	19±2

Initial development was taken direct compression for all the formulation and evaluated palatability study. ODT1, ODT2, ODT3 and ODT4 formulations are shown good palatability with direct compression method, but ODT5 & ODT6 were shown bitterness because direct compression process not suitable process for interaction of drug with taste masking agent. So wet granulation process was selected for ODT5 & ODT6 because drug and amberlite shown better interaction and good palatability were observed by volunteers.

Reference product was not available for granisetron hydrochloride, memantine hydrochloride, amlodipine besylate and zaleplon ODT formulations, but reference product was available in IR tablets and capsules form. The ODT in house tablets were shown higher drug release in first 10 min time point. Based on the above data, the ODT formulation shown lesser disintegration time and higher dissolution rate (Fig. 2).

Total eight formulation were prepared and conducted for taste evaluation study, in that one was positive control (placebo for granisetron hydrochloride ODT tablets, which contain all ingredients except drug), six formulas were test ODT formulations and one formula was negative control (risperidone is a highly bitter drug, so same formula were selected for negative control which contain all ingredients except taste and flavor enhancers like amberlite, aspartame, acesulfame potassium, menthol and peppermint flavor). The batches ODT1, ODT2, ODT3 and ODT4 were prepared using direct compression technique with aspartame, acesulfame potassium and peppermint flavor to study the different drugs effect on patient acceptability in terms of

palatability. The batches ODT5 and ODT6 were prepared using wet granulation technique with amberlite, citric acid, menthol, aspartame, acesulfame potassium and peppermint flavor to study the different drugs effect on patient acceptability in terms of palatability. Volunteer's acceptability of all the formulation were significantly similar with positive control in terms of mouth feel, taste, flavor and disintegration. Based on the patient evaluation study, taste masking agents, taste and flavor enhancers were sufficient in all formulations. Hence all the tested formulations were shown similar patent acceptability when compared with positive control.

Table 4: Overall summary report of taste evolution study report

Sr. No.	Formulations	Average points by volunteers	Acceptability	Rank
1	Positive control	99	Very Good	1
2	ODT1	98	Very Good	2
3	ODT2	91	Very Good	4
4	ODT3	87	Very Good	6
5	ODT4	98	Very Good	2
6	ODT5	88	Very Good	5
7	ODT6	81	Very Good	7
8	Negative control	10	Worst	8

Scale range: 81-100 – Very Good, 71-80 – Good, 61 – 70 – Acceptable, 41-60 – Poor, 11-40 – worst and 0-10 – not tolerable

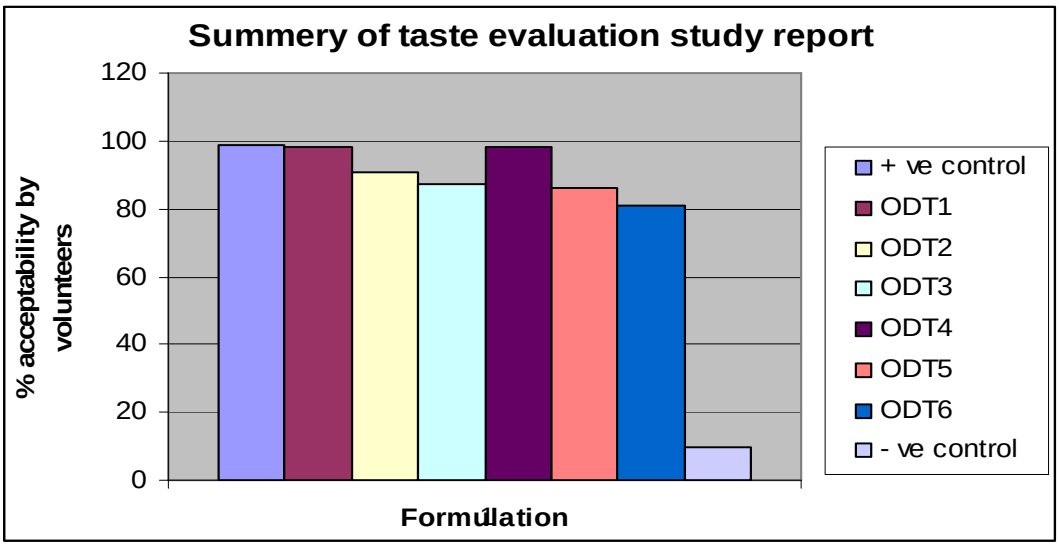

Fig 1: Graphical representation of taste evaluation study report

The results shown in Table 4 and Fig. 1 indicate that all the prepared formulation were similar interms of patient acceptability, it was observed in prepared formulations using peppermint flavor, menthol as a flavor enhancing agent, amberlite as a taste masking agent and Acesulfame potassium, aspartame as a taste enhancing agents are responsible for good acceptability by volunteers.

CONCLUSION

Oral disintegrating tablets (ODT) of different category drugs were successfully prepared by using compressed tablet process. Undoubtedly the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing, and rapid onset of action, fast disintegration, low side effect, good stability and its popularity in the near future. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the patient compliance and the absorption leading to its increased bioavailability. The prepared ODT formulations were to be administration by oral route at any time without need of water or any liquid vehicles. Hence ODT tablets are more suitable for at the time of travel, special cases or emergency conditions.

Granisetron hydrochloride, memantine hydrochloride, amlodipine besylate and zaleplon drugs are low bitter drugs with low dose. Simple taste and flavor enhancers with direct compression technique were sufficient to mask the bitterness these drugs. Risperidone and desloratidine are highly bitter drugs, so simple taste and flavor enhancers with direct compression technique were not sufficient to mask the bitterness. So additionally taste masking agents were applied to mask the taste of these products with granulation techniques. Hence for low bitter drugs taste masking by taste and flavor enhancers and taste masking agents required for highly bitter drugs.

Compressed tablet process would be an effective, low cost and simple alternative approach compared with the use of more expensive process like lyophilization and adjuvant in the formulation of oral disintegrating tablets.

Hence for low dose, low bitter drugs ware successfully prepared by simple direct compression method with taste and flavor enhancers and low dose highly bitter drugs like risperidone and desloratadine were prepared by wet granulation technique with taste masking agents to mask the bitterness of the drugs.

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