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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS FOR SELECTED ALZHEIMER DRUG

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ABSTRACT

Rivastigmine orally dispersible tablets were successfully manufactured according to the experimental procedure. Literature research and the trial and error method the quality of orally disintegrating tablets were selected. The tablets were found to have suitable physicochemical properties as well as desirable disintegration time and hardness. The Drug and polymer compatibility studies were examined DSC. Stability aspects of ODT formulations were evaluated using stability studies according to ICH guidelines and data complied with regulatory requirements. Orodispersible rivastigmine tablets have been successfully developed for Alzheimer's disease patients by direct compression technology. This technique is recommended by the US food and drug administration over similar solvent granulation techniques with the addition of superdisintegrants. This compounding process is faster and more economical than other techniques. His developed ODT formulation was compared with commercial products. The results were in good agreement with the disintegration time, wetting time and *in vitro* drug release profile. The developed ODT overcomes the problems of patient compliance, efficacy, side effects, weight gain and high cost associated with the use of conventional dosage forms in the treatment of Alzheimer's disease.

KEYWORDS

Orodispersible tablets, Rivastigmine, Alzheimer's patients and Immediate release.

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INTRODUCTION

Despite numerous innovations in drug delivery, including parenteral, transdermal and nasal, the oral route of administration remains the most common route. This is due to its various advantages such as the ease of ingestion, less pain, accurate dosage, self-medication potential, versatility, most essentially and patient compliance[1-3]. This is the

most commonly used mode of drug delivery and is generally considered the most convenient and economical as it has the lowest cost[4-8]. Due to these properties, oral administration is widely accepted by patients, accounting for up to 50-60% of all possible dosage forms. However, some drugs can cause gastrointestinal irritation. Difficulty swallowing conventional tablets is one of the main problems with this dosage form. Additionally, pediatric and geriatric patients also experience difficulty and inconvenience of swallowing. Sinced rinking water plays an important role in the swallowing of oral dosage forms, patients might experience an inconvenience to swallow the tablet when water is not available, such as in the case of motion sickness (kinetosis), sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[9-14].

Therefore, ODT is an excellent choice as a new drug delivery system due to its ease of administration and improved patient compliance, especially in the elderly and pediatrics. Orally disintegrating tablets are also very popular with active people who have no problems swallowing. Rapidly dissolving tablets are very fragile and brittle and require special peel-able blister packs. ODT technology has evolved very rapidly over the last decade. There is a new generation of his ODT that has been further developed to overcome the limitations of previous products[15,16]. Some companies have provided technological advances to produce pleasant-tasting tablets to overcome the common problem of bitter taste in drugs that undermines the benefits of ODT. Other companies have developed new techniques to improve the controlled release of ODT. The ease of manufacturing and reduced risks associated with rapidly dissolving tablets make ODT technology an excellent choice for most pharmaceutical manufacturing processes. Another factor that makes ODT so useful is the route of administration, which has hitherto been oral only. This one factor of his allows other companies to get approval for generic versions of their medicines[17,18.]

MATERIAL AND METHODS UTILIZED

Materials Used

Rivastigmine (Rachem ltd), Dibasic calcium phosphate dehydrate (Innophos), HPMC K100 M (Shin etsu), Eudragit RS PO (Evonik Degussa), Eudragit RL PO (Evonik Degussa), Povidone (ISP, U.S.A), PEG 20,000 (Clarient), Lubritab (JRS pharma), Lactose monohydrate (Rachem ltd), Cross povidone xl 10 (Rachem ltd), Magnesium stearate (Rachem ltd), Iso propyl alcohol (Rachem ltd), Opadry code (Colorcon) were purchased.

Instruments Used

Electrical balance (V-Tech), Multiple rotary punching machine (Rimek Phase-I), Vernier caliper (Mitutoya), Hardness tester (Monosanto), Friabilator (Nunes), Hydrolic press hardness tester (Dharma scientific products), Dissolution apparatus (Lab India), Sonicator (bath) (Remi equipment pvt Ltd), Dryer (Techno- Tray dryer), Micro centrifugator (Remi Rsearch Centrifugur), Micro syringe, Hot air ovan (NSW India), Bulk density test apparatus (Konark Instruments), Cyclo mixer (Rapid).

METHODOLOGY

Orodispersible tablets of selected drugs were manufactured by direct compression using three different approaches. Supercollapse addition, foaming, sublimation, and combination approaches according to prescribed recipes. One rivastigmine orodispersible tablet contains 4.0mg of the pure drug. A total tablet weight of 100mg was prepared for all formulations. Lactose monohydrate and mannitol were used as diluents for all formulations. For tablets made by the sublimation method, camphor is used as the sublimation agent. Sodium bicarbonate and citric acid were used for tablets manufactured according to the effervescent approach. For tablets manufactured using the superdisintegrant approach, crospovidone, croscarmellose sodium, and sodium starch glycolate were used as superdisintegrants. The indicated

amounts of drugs and other excipients were accurately weighed and passed through a 40# sieve prior to mixing. Magnesium stearate was individually passed through #60 mesh. The mixture was lubricated with magnesium stearate. The resulting powder mixture was compressed into tablets on a single punch tablet machine (Erweka, Germany) using 8mm flat punches. The compression force was adjusted to achieve a tablet hardness (2–4kg/cm3) within the range of pharmacopoeia for orally disintegrating tablets. In all formulations, weighed amounts of drug and lactose were mixed first, followed by thorough mixing of other excipients to load the drug onto the surface of the water-soluble carrier. Various formulations of rivastigmine have been developed through trial and error and are listed in Table No.1.

RESULTS AND DISCUSSION

Preformulation charecterstics of blend of all formulations

Preformulation study of the Blend - Bulk density, Compressibility index, Tapped density and Hausner's ratio are given in Table No.2.

Characterization of pure drug

The drug Rivastigmine and excipients for the research work were obtained from reliable sources. However, these drugs and excipients were scanned using FTIR as per procedure mentioned. Obtained infrared spectrum is comparable with standard spectrum, so the obtained drug and excipients from the commercial sources were genuine.

Drug excipient compatibility study

Unfavorable combinations of drug, drug and excipient may result in interaction, which leads to physical incompatibility or chemical incompatibility. Both physically and chemical instability may cause safety concerns. Hence, a thorough drug, drug/drug excipient compatibility study was performed as per procedure mentioned. At the end of 1st month, samples were assessment of chemical instability by Differential Scanning Calorimetry (DSC). The DSC thermograms corresponding to pure drug and drug excipient mixture were performed as per the procedure. It is therefore, expected the drugs and polymer are compatible with each other and free from any significant chemical interactions. The corresponding DSC spectra were displayed in Figures No.1.

In vitro release studies of developed Rivastigmine oral disintegrating tablets

A suitable *in vitro* dissolution method serves as a valuable quality control tool to assess batch to batch release performance and to assure the physiological availability of the drug. The *in vitro* dissolution test is also used to guide formulation development and to monitor manufacturing processes. As a regulatory test, it is used to approve minor changes in formulation, changes in the site of manufacturing and also to assess the scale up of the bio-batch to the production batch. All the batches have shown that as the disintegrant concentration increases. The drug release rates for rivastigmine orodispersible tablets were shown in Table No.3 and Figures No.2. However, the drug releases from these tablets were found to increase with increase in the concentration of disintegrant used in the formulation. Further the release rate was increased adding subliming agent and effervescent. The formulation contains high concentration of effervescent substance and crospovidone shows promising release rate within 20 mins compared to all other formulations. Thus, it can be concluded that *in vitro* release of drugs is a direct function of its solubility in the dissolution medium.

Table No.1: Composition of Rivastigmine orodispersible tablet

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Rivastigmine	04	04	04	04	04	04	04	04	04	04	04	04
2	Camphor	-	-	-	-	05	10	15	20	-	-	-	-
3	Sodium Bicarbonate	-	-	-	-	-	-	-	-	04	08	12	16
4	Citric Acid	-	-	-	-	-	-	-	-	04	06	08	10
5	Sodium Starch Glycolate	05	10	-	05	12	-	-	-	10	-	-	-
6	Croscarmellose sodium	05	05	10	-	-	08	-	-	-	08	-	-
7	Crospovidone	05	-	05	10	-	-	04	02	-	-	06	04
8	Lactose												
9	Mannitol	18	18	18	18	18	18	18	18	18	18	18	18
10	Aspartame	02	02	02	02	02	02	02	02	02	02	02	02
11	Talc	01	01	01	01	01	01	01	01	01	01	01	01
12	Magnesium Stearate	01	01	01	01	01	01	01	01	01	01	01	01
13	Total	100	100	100	100	100	100	100	100	100	100	100	100

Note: Ingredients weight were mentioned in mg

Table No.2: Preformulation charecterstics of blend of all formulations

S.No	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (θ)
F1	0.52±0.05	0.67±0.05	1.21±0.05	17.46±1.0	39.14±0.5
F2	0.57±0.05	0.61±0.05	1.35±0.05	19.04±1.0	38.97±0.5
F3	0.54±0.05	0.59±0.05	2.13±0.05	18.67±1.0	39.89±0.5
F4	0.53±0.05	0.55±0.05	1.89±0.05	20.00±1.0	41.32±0.5
F5	0.65±0.05	0.69±0.05	1.07±0.05	17.27±1.0	40.78±0.5
F6	0.55±0.05	0.54±0.05	1.59±0.05	19.76±1.0	39.88±0.5
F7	0.54±0.05	0.59±0.05	2.09±0.05	21.13±1.0	40.32±0.5
F8	0.51±0.05	0.71±0.05	1.77±0.05	19.96±1.0	38.86±0.5
F9	0.51±0.05	0.67±0.05	2.23±0.05	20.37±1.0	39.68±0.5
F10	0.49±0.05	0.51±0.05	1.69±0.05	19.86±1.0	39.95±0.5
F11	0.53±0.05	0.46±0.05	1.86±0.05	19.78±1.0	41.07±0.5
F12	0.48±0.05	0.59±0.05	1.98±0.05	17.89±1.0	40.99±0.5

Table No.3: *In-vitro* drug releasing profile (dissolution study)

S.No	Time (*min*)	Cumulative % Drug Release											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	2	16.9	15.9	19.9	18.7	20.2	20.9	22.3	18.9	22.9	28.8	21.7	19.5
3	4	23.3	22.8	25.9	24.6	27.2	28.5	29.3	25.2	27.6	38.4	26.8	25.5
4	6	29.8	26.7	29.3	28.4	33.1	35.4	39.4	31.2	35.6	45.7	32.9	31.9
5	8	35.9	34.2	37.4	36.8	39.2	38.2	52.6	38.5	42.5	57.8	39.2	38.3
6	10	49.7	42.1	46.2	43.4	43.9	42.7	66.2	43.6	46.7	69.4	46.4	43.6
7	12	57.8	56.7	50.8	49.4	51.2	50.3	73.8	51.1	52.2	78.3	53.1	52.8
8	14	68.2	66.4	64.7	57.6	59.7	58.3	84.5	57.6	59.5	88.9	62.4	59.7
9	16	83.8	79.8	78.8	71.2	73.8	74.2	90.3	73.7	76.9	93.8	71.8	78.9
10	20	89.6	92.5	90.6	88.6	89.3	93.4	94.9	85.1	86.8	99.1	90.6	87.2

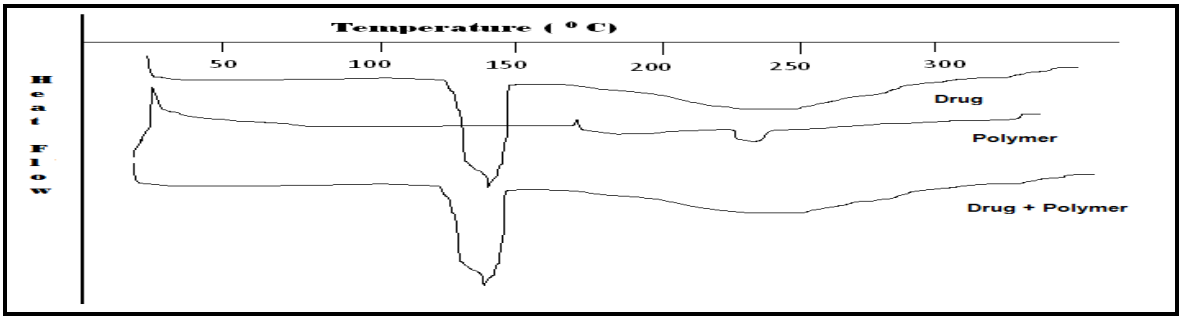
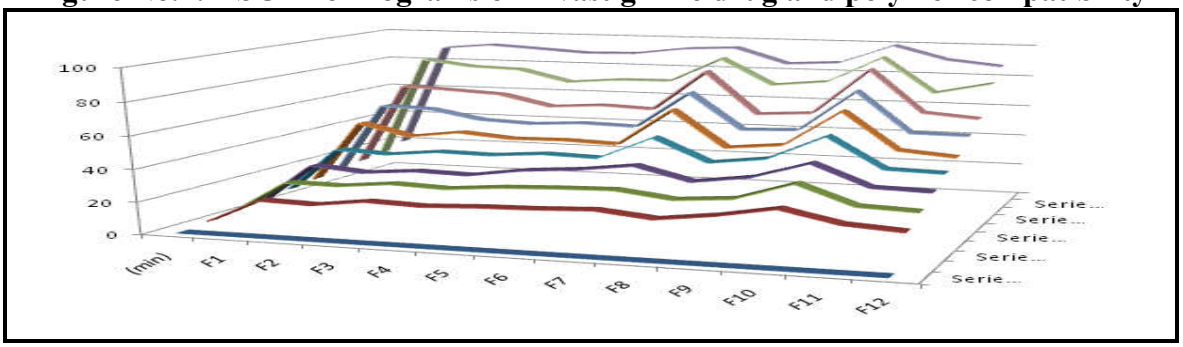


Figure No.1: DSC Thermograms of Rivastigmine drug and polymer compatibility



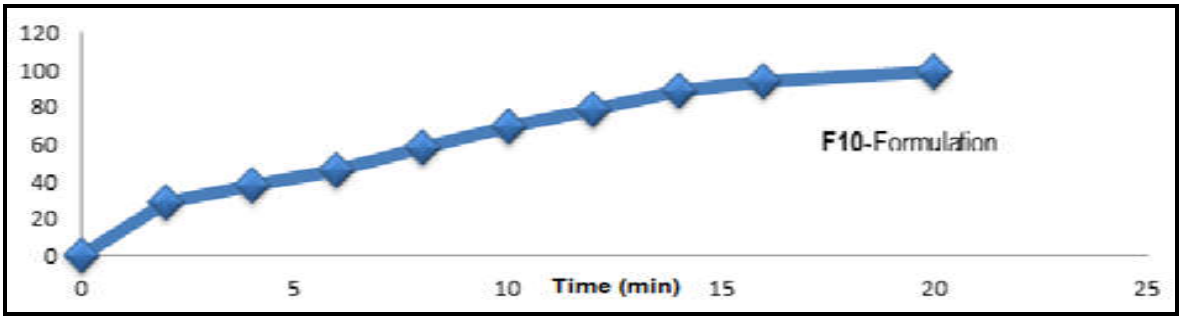


Figure No.2: Graphs of *in-vitro* drug releasing profiling [f-10 optimized formulation]

SUMMARY AND CONCLUSION

The DSC analysis of drug Rivastigmine alone elicited an endothermic peak at 132.3° C, which is very close to its reported melting point 128°C, where as mixture of Rivastigmine with Super disintegrants, Effervescence approach additives and Sublimation approach additives exhibited endothermic peak at 132.7°, 132.1º, 132.4ºC respectively. There was no significant changes in terms of peak shifting, appearance or disappearance of peaks were noted with the drugs, excipients and mixtures. Thus, it was thought to indicate the absence of chemical interaction between the selected drugs, and excipients. Absence of incompatibility between the selected drugs and polymers was also confirmed by the DSC pattern matching approach. The Rivastigmine orodispersible tablets were dissolved within 20 min and it's have very good bioavailability.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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