FORMULATION AND EVALUATION OF METOCLOPRAMIDE RAPIDLY DISINTEGRATING TABLETS

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ABSTARCT

Metoclopramide an effective antiemetic; acting on the CTZ, blocks apomorphine induced vomiting. Rapidly disintegrating tablets of metoclopramide hydrochloride were prepared by mass extrusion technique using three different superdisintegrants Sodium Starch Glycolate, Avicel Ph 102, L-HPC. Pre-compression parameters and post-compression parameters were evaluated for all the nine formulations. Angle of repose and % compressibility showed good flowability in all the formulations. Weight variation was found within limits and drug content of all the formulations was found in the range of 9.700 mg - 9.925 mg in each tablet. The hardness of all the formulations was almost uniform and possessed good mechanical strength with sufficient hardness. The wetting time in all the formulation was fast. Formulations F3 containing sodium starch glycolate 10% & F6 containing Avicel ph 102 10% tablets disintegrated rapidly to release the drug. *In vitro* release studies revealed that 96% of drug releases from SSG, MCC (90%), and L-HPC (85%) for all the formulations were within 15 min. Based on above results, three formulations F3, F6, F9 were selected for stability studies these formulations showed not much variation in any parameter even after the period of 30 days, formulations F3, F6, F9 are found to be stable and retained their original properties. Thus, it may be concluded that formulation containing sodium starch glycolate as superdisintegrants is fulfilling all the parameters satisfactorily. It showed excellent *in vitro* disintegration, *in vitro* dispersion time, compared to other superdisintegrants. And the rapidly disintegrating tablets can be prepared by mass extrusion technique

Keywords: Rapidly disintegrating tablets; Sodium starch glycolate, Microcrystalline cellulose, Mass extrusion

INTRODUCTION

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular dosage forms are being tablet and capsules, one important drawback of these dosage forms for some patients however is the difficulty in swallowing.[1] Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis.[2] For these reasons, tablet which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving or disintegrating tablet are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[3] Recently Pharmaceutical industry has become increasingly aware of the need that elderly be considered as a separate and unique medicare population. Though geriatric patients constitute a minor proportion of the population, its growth rate is high and hence will have significant impact on development of drug delivery systems. Thus mouth dissolving tablet are gaining more demand and popularity from last few years.[4] Mouth dissolving tablets are those when put on tongue, disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Faster the drug into solution the quicker the absorption and onset at clinical effect. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.[5] Metoclopramide is chemically related to procainamide. It is a gastric hurrying agent; it is now a widely used antiemetic. It has more permanent effect on upper G.I.T, increases gastric peristalsis while relaxing the pylorus and the first part of deuodenum. Metoclopramide is an effective antiemetic; acting on the CTZ, blocks apomorphine induced vomiting. Metoclopramide acts through both dopaminergic and serotonergic receptors. Metoclopramide is rapidly absorbed orally, enters brain, crosses placenta and is secreted in milk. It is partly conjugated in liver and excreted in urine within 24 hours. Half life of Metoclopramide is 3-6 hours. Orally it acts in 30 m -1 h, but within 10 m after I.M. and 2 m after I.V. injection and lasts upto 4-6 h. It hastens the absorption of many drugs, e.g. Aspirin, Diazepam etc. by facilitating gastric emptying.[6] The principle of the present investigation is to develop and characterize rapidly disintegrating tablets, which disintegrates in the oral cavity in a matter of second without the need of water. This helps in easy swallowing thereby improved clinical effects through pregastric absorption, leading to an increase in bioavailability of the drug and quick onset of pharmacological action can take place.

MATERIALS AND METHODS

Metoclopramide hydrochloride was a gift from Cosme Pharmaceuticals., Goa. Sodium Starch Glycolate,

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Microcrystalline cellulose and L-HPC was a kind gift sample from Kawaralal and Company, Mumbai, Reliance Cellulose Products & Aristo Pharmaceuticals Ltd., and Bhopal respectively. All other chemicals purchased from S.D Fine Chemicals, Mumbai, were of analytical reagent grade.

Preparation of Metoclopramide Hydrochloride Rapidly Disintegrating Tablets by Mass Extrusion Technique [7]:

The drug is mixed with powdered Eudragit E-100 in a suitable ratio. Then 10% ethanol is added to the above mixture in a glass beaker. The consistency of the above solution is reduced to get gel type of preparation, and then it is extruded through a syringe on clean glass slab. After extrusion of the gel, dried overnight till ethanol is evaporated and solidified material (gel) crushed into granules using a mortar. The granules are passed through a sieve and collected, blend with Avicel PH 102, L-HPC, sodium starch glycolate, lactose, magnesium stearate and talc as in Table 1. Then blend is subjected for tablet formulation.

Table 1: Composition of rapidly disintegrating tablets of Metoclopramide Hydrochloride

Ingredients (mgs)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoclopramide Hcl	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	15	22.5	30	--	--	--	--	--	--
Avicel PH 102	--	--	--	15	22.5	30	--	--	--
Low hydroxyl propyl cellulose	--	--	--	--	--	--	15	22.5	30
Eudragit E-100	10	10	10	10	10	10	10	10	10
Lactose	259	251.5	244	259	251.5	244	259	251.5	244
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3

Physical Evaluation of Metoclopramide Hydrochloride Rapidly Disintegrating Tablets:

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed. Percent compressibility of powder mix was determined by Carr's compressibility index calculated by following equation[8]. Carr's Index %= 100 (TBD-LBD)/TBD, where TBD and LBD are the Tapped bulk density and Loosed bulk density respectively.

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light. Three tablets were picked from each formulation randomly and thickness was measured individually. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan). Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester[9]. Three tablets were randomly picked and hardness of the tablets from each formulation was determined. The friability of tablets was determined using Roche Friabilator.

Drug content was calculated by weighing & crushing one tablet. The whole amount of powdered tablet was transferred into a 100 ml volumetric flask. Add 0.1N HCl up to the mark. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 2ml of filtrate was taken in a 25 ml volumetric flask and diluted up to the mark with 0.1N HCl and analyzed spectrophotometrically at 305 nm. The concentration of Metoclopramide hydrochloride (in µg/ml) was calculated by using the standard calibration curve of Metoclopramide hydrochloride. Drug content claim was 10mg per tablet. This procedure was followed for 5 tablets from each formulation.

Following method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small petridish (i.d. = 6.5 cm) containing 6 ml of water, a tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined. A piece of tissue paper folded twice was placed in a small Petridish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation[10] R = 100 x (Wa – Wb)/Wb Where, Wb = weight of the tablet before water absorption and Wa = weight of the tablet after water absorption respectively.

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed. Standard deviation was also determined and it is expressed in seconds[11].

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. *In vitro* release studies were carried out using tablet dissolution test apparatus USP XXIII[12]. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established. In the present study, stability studies were carried out at 25° / 60 % RH and 40° / 75 % RH for a specific time period up to 30 days for selected formulations[13].

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RESULTS AND DISCUSSION

The values for angle of repose were found to be in the range of $25^0.22'$ to $30^0.17'$. All formulations showed the angle of repose within 30^0. This percent compressibility of powder mix was determined by Carr's compressibility index. The percent compressibility for all the nine formulations lies within the range of 12.676 to 17.808. All formulations are showing good compressibility. Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for color. Tablets showed flat, circular shape in white color.

The thickness of the tablets was measured by using dial caliper by picking the tablets randomly. The values are almost uniform in all formulations. Thickness was found in the range from 2.90 mm to 3.18 mm respectively. The results of hardness are given in Table 2. Hardness test was performed by Monsanto tester. Hardness was maintained to be within 2.90 kg/cm^2 to 4.16 kg/cm^2, as these tablets are rapidly disintegrating. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The percentage weight variation for all the formulation is tabulated in Table 2. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ± 7.5%. It was found to be from 298.6 to 301.0 mg. The weight of all the tablets was found to be uniform. The content uniformity was performed for all the nine formulations and results are shown in Table 2.

Table 2: Evaluation of tablet parameters

Formulation Code	Uniformity of Thickness (n=3) (mm)	Hardness (n=3) (kg/cm^3)	% Friability (n=10)	Weight Variation (n=10) (mg)	Drug Content (n=3) (mg)
F1	3.13±0.05	3.87±0.29	0.3633	301.0±2.013	9.790±0.148
F2	3.17±0.06	3.76±0.29	0.2103	300.5±2.153	9.825±0.113
F3	3.18±0.05	3.70±0.29	0.1356	300.5±2.652	9.925±0.067
F4	2.97±0.03	3.76±0.29	0.3496	298.6±2.88	9.889±0.176
F5	3.13±0.05	3.24±0.29	0.3035	300.0±1.032	9.900±0.031
F6	3.15±0.13	3.66±0.29	0.2103	300.1±1.272	9.918±0.021
F7	2.90±0.05	3.24±0.29	0.4739	300.1±2.171	9.700±0.148
F8	2.97±0.03	2.96±0.29	0.4200	299.4±3.045	9.835±0.113
F9	2.98±0.03	2.90±0.29	0.4187	299.6±2.197	9.876±0.054

Five trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets were found between 9.700 ± 0.148 mg to 9.925 ± 0.067 mg of metoclopramide hydrochloride. The results indicated that in all the formulations the drug content was uniform. The cumulative percentage drug released by each tablet in the *in vitro* release studies were based on the mean content of the drug present in the respective tablet.

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. This was determined as per I.P. for all the formulations. All formulations showed disintegration time less than 25 seconds. Sodium starch glycolate disintegrates faster (8sec) as compared to other superdisintegrants. Wetting is closely related to inner structure of tablets. The record of the wetting time was shown in Table 3. The wetting time in all the formulation was very fast. This may be due to ability of swelling and also capacity of absorption of water. Sodium starch glycolate is having high water absorption capacity and cause swelling. SSG and MCC absorb water rapidly in the formulations and shows fast wetting time. This parameter also duplicates disintegration time in oral cavity as tablet is kept motionless on tongue; hence correlation between wetting time and disintegration time in oral cavity can also be made. The water absorption ratio results are tabulated in Table 3

Table 3: Wetting time, water absorption ratio

Formulation Code	Wetting Time (n=3)	Water Absorption Ratio (n=3)
	Mean ± SD	*Mean ± SD*
F1	22.00 ± 1.12	27.81 ± 1.123
F2	18.00 ± 0.67	19.84 ± 0.663
F3	17.33 ± 1.55	18.45 ± 2.135
F4	24.67 ± 0.36	30.89 ± 1.637
F5	23.67 ± 0.55	29.89 ± 1.653
F6	22.33 ± 1.57	28.08 ± 1.428
F7	28.33 ± 0.59	37.89 ± 1.345
F8	26.00 ± 1.01	36.37 ± 1.965
F9	25.33 ± 0.59	34.09 ± 1.936

The ratio values of formulations found in the range of 18.45 to 37.89. In this, as L-HPC quantity decreases, the water absorption also decreases due to less swelling property. *In vitro* dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion within 25 seconds observed in all the formulations. This

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indicates the Sodium starch glycolate showed best disintegrant in the prepared tablets as compared to Avicel PH 102 and L-HPC. This *in vitro* dispersion time gives direct information regarding super-disintegrating nature of disintegrants used.

All the nine formulations were subjected for the *in vitro* dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed at 305 nm. Cumulative drug release and cumulative % drug retained were calculated on the basis of mean amount of metoclopramide hydrochloride present in the respective tablet. Formulation F1, F2, F3, releases 89.83%, 91.10%, 96.20%, respectively, at end of 15 minutes. The rapid drug dissolution was observed in F4, F5, and F6, which release 85.11%, 88.71% and 90.44% respectively at end of 15 minutes. Formulation F7, F8, F9, releases 78.26%, 82.26%, 85.31%, respectively, at end of 15 minutes. This rapid dissolution might be due to fast breakdown of particles and rapid absorption of drug. The drug release was completely achieved in a shorter duration of time. In all the formulations the drug release was near to 90% within 15 minutes shown in Table 4

Table 4: *In vitro* disintegration time, *in vitro* dispersion time

Formulation Code	*In vitro* Disintegration Time (Sec)(n=3)	*In vitro* Dispersion Time (sec.) (n=3)
F1	11.67 ± 2.082	20.00 ± 1.11
F2	09.33 ± 1.143	18.33 ± 0.56
F3	08.00 ± 1.023	14.33 ± 1.24
F4	19.30 ± 0.556	21.67 ± 0.65
F5	18.33 ± 0.567	19.67 ± 0.67
F6	16.33 ± 0.587	15.33 ± 1.25
F7	23.67 ± 0.556	23.67 ± 1.23
F8	19.33 ± 0.545	21.67 ± 0.65
F9	17.33 ± 0.567	20.00 ± 1.11

High dissolution may also occur due to faster breakdown. F4, F5, F6, F7, F8 and F9 showed release variation probably due to slow breakdown of particles. In comparative study for the formulations F3, F6, F9 releases 96.20%, 90.44%, 85.31% respectively at the end of 15 minutes, and graphical representation is shown in figure 1.

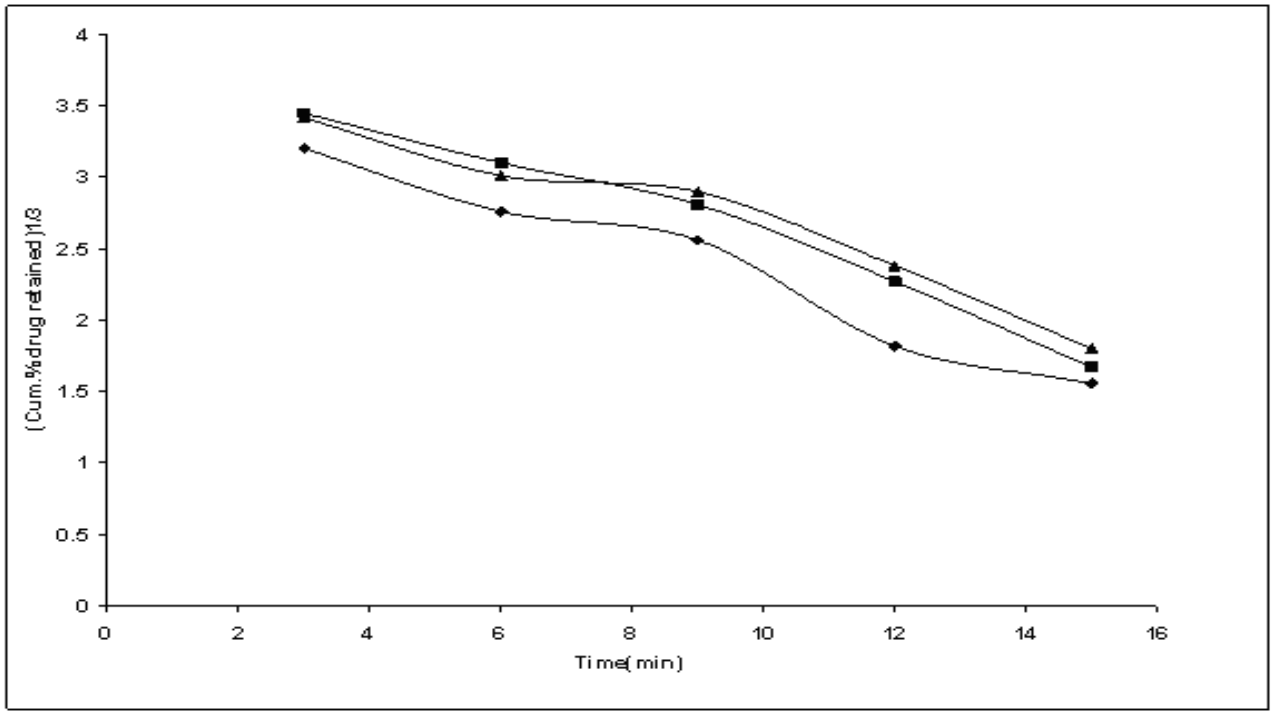

Figure 1: Comparative *in vitro* Release Profile of Metoclopramide Rapidly Disintegrating Tablets for Formulation F-3, F-6 & F-9.release profile of formulation F-3 containing 10% w/w SSG (◆),of formulation F-6 containing 10% w/w MCC (■), of formulation F-9 containing 10% w/w L-HPC (▲).

Next, the model fitting of the release profiles were performed using PCP DISSO-V2 software to observe the mechanism. The correlation coefficient values obtained for F3, F6, and F9 formulations shows Hixson Crowell model which are shown in figure 2.

The formulations F3, F6, F9 were selected for stability studies on the basis of their high cumulative % drug release and also results of *in vitro* disintegration time, wetting time, and *in vitro* dispersion studies.

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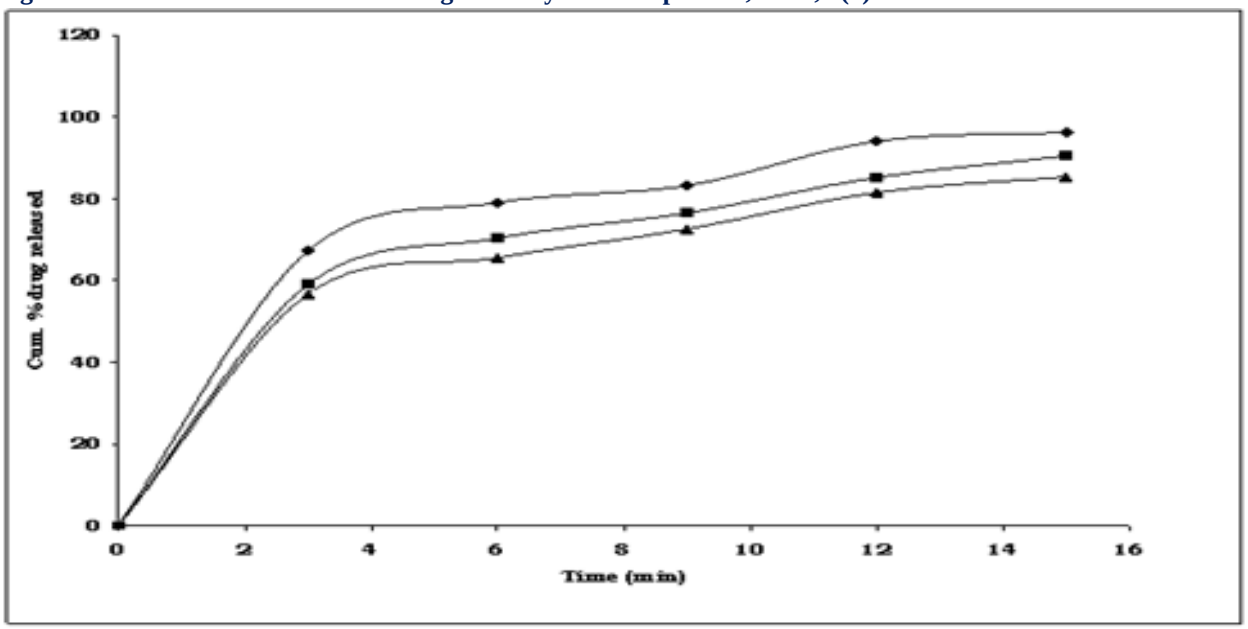

Figure 2: Comparative *in vitro* Release Profile of Metoclopramide Rapidly Disintegrating Tablets According Hixson Crowell Equation for Formulation F-3, F-6 & F-9. release profile of formulation F-3 containing 10%w/w SSG(◆), of formulation F-6 containing 10% w/w MCC (■), of formulation F-9 containing 10% w/w L-HPC (▲).

The stability studies were carried out at 25°/ 60% RH and 40°/ 75% RH for all the selected formulations up to 30 days. For every 10 d time interval the tablets were analyzed for drug content uniformity, hardness, in vitro disintegration time, friability and wetting time up to 30 d. These formulations showed not much variation in any parameter. From these results it was revealed that, formulations F3, F6, F9 are stable and retained their original properties.

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REFERENCES:

1. Indurwade NH, Rajyaguru TH, Nakhat PD. Novel Approach - Fast Dissolving Tablets. Indian Drugs 2002;39(8): 405-9.
2. Watanabe Y, Koizumi K, Zama Y, Matsumoto Y, Motsumoto M. New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Biol Pharm Bull 1995;18(9): 1308-10.
3. Bi Y, Yonezawa Y, Sunada H. Rapidly disintegrating tablets prepared by the wet compression method: Mechanism and Optimization. J Pharm Sci 1999;88(10): 1004-10.
4. Yeola BS, Pisal SS, Paradkar AR, Mahadik KR. New drug delivery system for elderly. Indian Drugs 2000;37(7): 312-8.
5. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets; A novel drug delivery systems. Pharma Times June 2003;35 : 7-9.
6. Tripathi KD. Essentials of Medical Pharmacology, 5th Ed. New Delhi : Jaypee Brothers Medical Publishers (P) Ltd; 2003.
7. Ishikawa T, Watanabe Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste-masked granules by the compression method. Chem Pharm Bull 1997;47(10): 1451-1454.
8. Subramanyam CVS. Textbook of Physical Pharmaceutics, Vallabh Prakashan, 2nd ed; 2001.
9. Mehta RM. Pharmaceutics-I, Vallabh Prakashan, 2nd ed; 1997.
10. Yunxia B, Hisakazu S, Yorinobu Y, Kazumi D, Akinobu O, Kotaro I. Preparation and evaluation of compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull 1996;44(11): 2121-2127.
11. Redkar MR, Gore SP, Devarajan PV. D-Zolv taste masked mouth dissolve tablets. Indian J Pharm Sci 2002;64(3): 291-292.
12. "In vitro Dissolution" The United States Pharmacopoeia, United States Pharmacy Convention, Inc. Asian edition, 2000;1941-1943.
13. Natalie MC Clure. Stability studies in overview of ICH Guidelines for Drug Products. Matrix Pharmaceutical Inc, 1997. (http://www.mcclurenet.com).

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