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FORMULATION AND *IN-VITRO* EVALUATION OF FAST DISSOLVING TABLETS OF CANDESARTAN CILEXETIL

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1. INTRODUCTION

These are novel types of tablets that disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bed-ridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.[1-2]

1.1 Ideal properties of a mouth dissolving tablet[3-4]

A mouth dissolving tablet should:

1. Not require water or other liquid to swallow.
2. Easily dissolve or disintegrate in saliva within a few seconds.
3. Have a pleasing taste.
4. Leave negligible or no residue in the mouth when administered.
5. Be portable and tolerate the transportation stress.
6. Be able to be manufactured in a simple conventional manner within low cost.
7. Be less sensitive to environmental conditions like temperature, humidity etc.

1.2 Advantages of mouth dissolving tablet[5-6]

1. No need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. Accurate dosing as compared to liquids.
4. Dissolution and absorption of drug is fast, offering rapid onset of action.

5. Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva, passing down into the stomach.
6. Advantageous over liquid medication in terms of administration as well as transportation.
7. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
8. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.

1.3 Techniques for preparing mouth dissolving tablets[7-9]

1.3.1 Freeze drying: A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. However, the use of freeze-drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

A tablet that rapidly disintrigrants in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amount of saliva.

1.3.2 Moulding: Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution.

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is, in general, made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

1.3.3 Sublimation: Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Inert solid ingredients (ex. urea, urethane, ammonium carbonate, camphor, naphthalene) are added to other tablet excipients and the blend is compressed into tablet. Removal of volatile material by sublimation generated a porous structure.

A method of producing fast dissolving tablet using water as the pore forming material has been described by Makino, et al. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Koizumi, et al, have developed a new method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material.

1.3.4 Spray-Drying: Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. Spray drying technique has been employed by Allen and Wang to prepare fast dissolving tablets. They developed formulation by using mannitol as bulking agent, hydrolysed and non-hydrolysed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (ex. citric acid) and/or alkali material (ex.$NaHCO_3$) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds.

1.3.5 Mass-Extrusion: This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

1.3.6 Direct Compression: It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually

required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

The simultaneous presence of disintegrate with a high swelling force called disintegrating agent and substances with low swelling force (starch, cellulose and direct compression sugar) defined as, "swelling agent" was claimed to be a key factor for rapid disintegration of tablet, which also offers physical resistance.

2. MATERIAL AND METHODS

According to the research design, candesartan cilexetil has been provided by Triveni Interchem Private Limited. Moreover, polymers crospovidone (Salvi Chemical Industries Limited) was selected as superdisintegrant and micro crystalline cellulose as binder have been provided through (Spechem Cellulose Private Limited).

The equipment used were tablet punching machine, friabilator, hardness tester, dissolution apparatus, disintegration apparatus, pH meter, double beam UV spectrophotometer, digital micrometer, bulk density apparatus, infra-red spectrophotometer.

3. RESULTS AND DISCUSSION

3.1 Analysis of Candesartan Cilexetil

3.1.1 Determination of Absorption maxima (λ_{max}) of Candesartan Cilexetil

λ_{max} of Candesartan Cilexetil in Phosphate Buffer (pH 6.8) was found to be 253 nm.

3.1.2 Calibation Curve of Candesartan Cilexetil

Calibration curves were constructed in phosphate buffer (pH 6.8). Beer's law was obeyed in the concentration range of 10-100 µg/ml. The high values of regression coefficient(0.9995) estimated the linearity of relationship between concentration and absorbance.

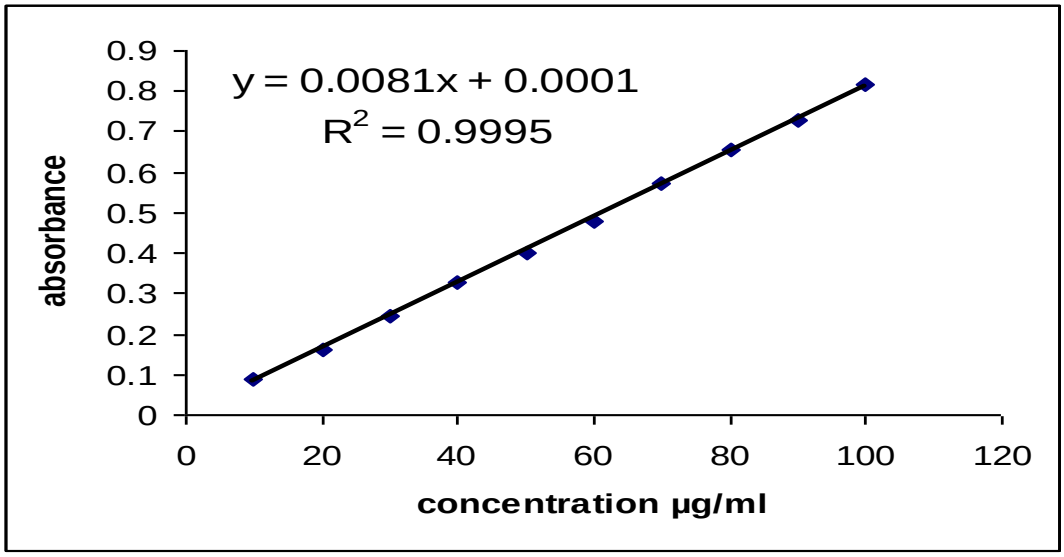

Fig. 1: Calibration curve of Candesartan Cilexetil in Phosphate Buffer (pH 6.8)

3.1.3 Solubility

Solubility of candesartan cilexetil was determined in different solvents and the observations are shown in Table. The maximum solubility was found in DMSO and least in water.

Table 1: Solubility Profile of Candesartan Cilexetil.

S. No.	Solvents	Solubility
1.	Distilled water	+
2.	0.1N Hydrochloric acid	+
3.	Ethanol	++
4.	Methanol	++++
5.	DMSO	+++++

Practically insoluble + Slightly soluble ++

Freely soluble +++++ Soluble ++++

3.1.4 Partition coefficient

Partition coefficient of Candesartan Cilexetil in n-octanol and Phosphate buffer pH 6.8 was found to be 4.93.

3.1.5. Differential Scanning Calorimetry

The thermogram of Candesartan Cilexetil shows a sharp endothermic peak at 182.51°C corresponding to melting of pure drug and its crystalline nature. The thermogram of Tulsion 335 indicates its amorphous nature. The thermogram of DRC indicates its amorphous nature and shows the absence of endothermic peak of melting of the drug. The formation of DRC

and entrapment of Candesartan Cilexetil in the polymer matrix of Tulsion 335 was thus confirmed from the findings of these three studies.

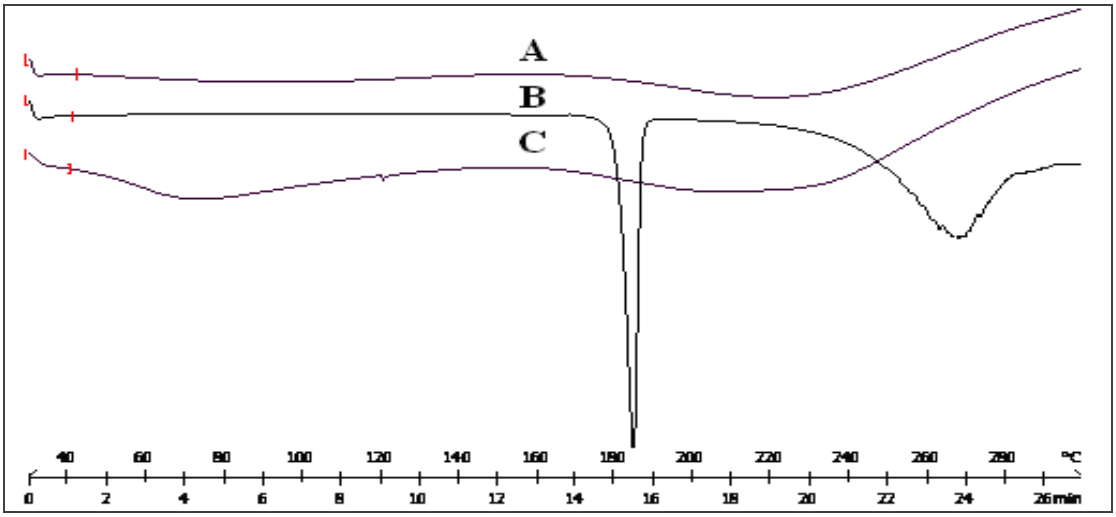

Fig. 2: DSC thermograms of (A) Tulsion335, Candesartan Cilexetil(B) and DRC(C)

3.2 Taste Masking of Candesartan Cilexetil

3.2.1 Determination of threshold bitterness concentration of Candesartan Cilexetil

Threshold bitterness concentration is the minimum concentration at which bitterness starts to appear and continues to provoke after 30s. Most of the volunteers rated 20 µg/ml as the threshold bitterness concentration for Candesartan Cilexetil. It was concluded that the taste masked form of the drug should not release more than or equal to 20 µg/ml of the drug in mouth within 2 minutes for satisfactory taste masking.

Table 2: Rating by the volunteers for different solutions of Candesartan Cilexetil on the scale of bitterness (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness)

Volunteer No.	Rating on the scale of bitterness				
	10µg/ml	20µg/ml	30µg/ml	40µg/ml	50µg/ml
1.	0	0	1	1	2
2.	0	1	2	2	3
3.	1	1	2	2	3
4.	0	1	2	2	3
5.	0	1	1	2	3
6.	0	1	2	3	3
7.	0	1	2	2	3
8.	0	0	1	1	2
9.	0	1	2	2	3
10.	0	1	1	2	3

3.2.2 Selection of method for taste masking of Candesartan Cilexetil

The taste masked form of the drug should release the drug quickly in gastric juice but not in saliva. For mouth dissolving tablets, mouth feel is as important factor as the taste masking. The tablet should not disintegrate into large particles that cause gritty feel. Considering these criteria, granulation and coating of the drug as well as microspheres were not selected as approaches for taste masking. Granulation and coating of the drug may also get ruptured or fractures by compression forces and chewing. So initially three approaches namely, inclusion complexes, ion exchange complexes and solid dispersions were investigated.

A. Taste masking by formation of inclusion complexes with BCD

Inclusion complexes of Candesartan Cilexetil with BCD were prepared in 1:1 and 1:2 molar ratios using kneading method. Kneading method was selected as it is simpler and less time consuming than the solvent evaporation method. It was observed that the inclusion complexes were not able to mask the bitter taste of Candesartan Cilexetil. This observation may be attributed to the high solubility of BCD in water and saliva which releases the drug rapidly in the mouth.

B. Taste masking by preparing solid dispersions

Solid dispersions of Candesartan Cilexetil in PEG (4000, 6000) and Eudragit (E100, EPO) were prepared by melt solidification method and solvent evaporation respectively. PEG was not able to mask the bitter taste. Solubility of these polymers in water results in the release of drug which causes bitterness. Eudragit E100 and EPO are not soluble at salivary pH, still could not mask the bitter taste. This was due to poor entrapment of the drug in the polymer matrix. The drug was not properly enclosed in the polymer matrix and caused bitter sensation as it was exposed to the taste buds.

C. Taste masking by formation of complexes with ion exchange resins

Batch process was used to load Candesartan Cilexetil on the ion exchange resins (1:1 drug: resin ratio) in the preliminary trials. Indion resins (204, 214, 234, 294 and 464) were showed very small loading of the drug (< 15%) and poor taste masking. Tulsion 339 showed improved taste masking but low values of drug loading (<30%). Tulsion 335 showed excellent taste masking and high drug loading (95%). The process was repeated five times to check reproducibility of the results and showed a small variation (standard deviation ± 0.94). Based on these preliminary studies, Tulsion 335 was selected for masking the bitter taste of Candesartan Cilexetil.

3.3 Characterization of drug resin complex (DRC)

3.3.1 Taste evaluation

***In-vitro* taste evaluation**

The objective for this test was to check whether the DRC releases any drug at salivary pH during a time interval of 300 s. No detectable amount of Candesartan Cilexetil dissolved in the phosphate buffer of pH 6.8 was detected at the end of 300 s. Thus the DRC did not release any drug at salivary pH.

3.3.2 Determination of drug content

When DRC was prepared using all of the optimized parameters for drug loading, the percent drug loading was found to be 96.24% and hence the drug content was 48.14% w/w.

3.3.3 *In-vitro* dissolution studies

The dissolution profile of DRC showed complete drug release within 20 minutes in 0.1 N HCl. Thus DRC releases the drug quickly upon contact with acidic environment although it does not release any drug at salivary pH. The rate and completeness of drug release is controlled by the diffusion rate of the drug through the polymer phase of the resin, (usually a function of molecular weight), the selectivity of the drug for the resin, and the concentration of electrolytes particularly in the hydrogen ion, in the surrounding environment. More hydrophobic drugs will usually elute from the resin at a lower rate, as will drugs with a relatively high selectivity for the carboxylic acid functional structure in the resin. Candesartan Cilexetilis eluted rapidly from the DRC because of its highly hydrophilic nature and having low selectivity for the carboxylic acid functional groups of the resin.

3.4 Selection of levels of materials

Crospovidone showed good disintegration activity in the concentration range of 3-9 % w/w. An increase in quantity of crospovidone required more quantity of water for fast disintegration. The work was focused on fast disintegration of the tablet in a small quantity of water (6 ml) to simulate the small quantity of saliva available in the mouth. Levels of Micro Crystalline Cellulose were fixed at 4-8% w/w. Levels above this range of Micro Crystalline Cellulose definitely increased the mechanical strength but disintegration of the tablet was delayed. This was observed because of increase in the wetting time of the tablets. The disintegration process is started by wetting of the tablets and depends on both the factors. Crospovidone causes disintegration by a fast water wicking process and Micro Crystalline Cellulose separating the particles by melting and thereby disintegrates the tablet.

3.5 Evaluation of tablet blends

The 9 tablet blends prepared were analyzed for various micromeritic and flow properties. Values of compressibility index were less than 15. Hausner ratio was between 1 and 1.17. Angle of repose was less than 30°. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The outcomes of these parameters indicated excellent flow properties and the blends were suitable for direct compression.

3.5.1 Physical evaluation

The tablets were within limits of weight variation allowed by I.P. 1996. Hardness of the tablets was within 3.5- 4 kg/cm^2 which indicated adequate mechanical strength. Diameter of the tablets was close to 8 mm (7.9-8). Thickness varied from 2.5-2.8 mm.

3.5.2 Disintegration time

According to the European pharmacopoeia the fast disintegrating/ Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. However it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of test solution compared to the volume of saliva in humans, which is limited to a few ml. Thus the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. To overcome these problems, several methods have been proposed. In this work, disintegration time was assessed by a simplest method. 6 ml of phosphate buffer of pH 6.8 that simulated the volume and pH of saliva present in mouth was taken in a 25 ml measuring cylinder at 37±2°C and a MDT was placed in it. Time required for complete disintegration of the tablet was recorded as DT. It was observed that DT decreased from formulation A1 to A9. Increase in the levels of crospovidone and Gelucire had negative effect on DT i.e. DT decreased with increase in the levels of both factors. Crospovidone is known for rapid disintegration activity due to fast water wicking action. Gelucire 39/01 also aided in the disintegration process by melting at the test temperature.

3.5.3 Friability

Friability of the tablets was found to decrease with an increase in the concentration of both factors. Micro Crystalline Cellulose being a binder, decreases friability. Crospovidone is also known to produce mechanically strong tablets.

Thus both the factors had desired effects on disintegration time and friability. These effects were further analyzed using statistical models.

3.5.4 Wetting time

Wetting time for the tablet formulations was found to vary in the range 9-40s. It was observed that the disintegration process was started by wetting of the tablets.

3.5.5 Dissolution studies

The dissolution profiles of all 9 trial batches showed complete release of the drug within 20 minutes which was similar to the release profile from DRC. It was observed that there was no variation in dissolution profiles among the tablet formulation and the factors under study had no effect on the drug release. As all the tablets disintegrated completely in less than 1 minutes, drug release was solely controlled by desorption of the drug from DRC.

Table 3: Evaluation of physical properties of tablet blends.

Formulation Code	Bulk density (gm/ml)±SD	Tapped Density (gm/ml)±SD	Hausner ratio	Compressibility index	Angle of repose
A1	0.8294±0.02	0.9296±0.03	1.1208	12.08	27.78±0.03
A2	0.8626±0.03	0.9036±0.04	1.0475	4.75	28.08±0.02
A3	0.8439±0.04	0.9156±0.01	1.0849	8.49	26.06±0.04
A4	0.8321±0.02	0.9221±0.02	1.1081	10.81	24.67±0.01
A5	0.8284±0.02	0.9286±0.04	1.1209	11.96	25.55±0.02
A6	0.8675±0.02	0.9135±0.02	1.0530	5.30	27.08±0.01
A7	0.845±0.02	0.9916±0.01	1.1734	9.67	25.06±0.01
A8	0.864±0.02	0.9234±0.04	1.0687	11.73	23.67±0.02
A9	0.8221±0.03	0.9247±0.02	1.1248	12.48	24.85±0.01
Broad range	0.8221-0.8675	0.9135-0.9916	1.0530-1.1248	4.75-12.48	23.67-28.08

n=3

Table 4: Physical Evaluation of tablet formulations.

Formulation Code	Weight Variation (mg)±SD	Hardness (kg/cm^2) ±SD	Diameter (mm) ±SD	Thickness (mm) ±SD
A1	250.31 ± 1.61	3.5 ± 0.23	8 ± 0.05	2.5 ± 0.02
A2	250.19 ± 1.32	3.6 ± 0.52	8 ± 0.04	2.7 ± 0.03
A3	250.42 ± 1.47	3.6 ± 0.29	8 ± 0.03	2.8 ± 0.04
A4	149.92 ± 1.46	3.7 ± 0.52	8 ± 0.00	2.7 ± 0.02
A5	250.89 ± 2.11	3.7 ± 0.59	7.9 ± 0.05	2.5 ± 0.01
A6	250.33 ± 1.68	3.8 ± 0.76	8 ± 0.03	2.6 ± 0.02
A7	251.06 ± 1.20	3.8 ± 0.72	8 ± 0.02	2.8 ± 0.05
A8	149.86 ± 1.42	3.9 ± 0.53	8 ± 0.04	2.8 ± 0.03
A9	250.63 ± 1.63	4.0 ± 0.28	8 ± 0.02	2.7 ± 0.04
Broad range	149.86 - 250.89	3.5-4	7.9 - 8	2.5 - 2.8

n=3

Table 5: Evaluation of various parameters of tablets.

Formulation Code	Disintegration Time (s) ± SD	Wetting time(s) ± SD	Friability ± SD%	% Assay ± SD
A1	54±1.02	40±0.94	1.02±0.02	98.64±1.02
A2	48±0.89	38±0.57	0.88±0.01	99.21±1.26
A3	42±1.21	34±1.21	0.8±0.04	99.42±0.85
A4	36±0.67	28±0.68	0.73±0.02	98.41±0.62
A5	30±0.96	21±0.59	0.66±0.03	98.53±1.08
A6	25±0.82	19±0.74	0.60±00.02	98.02±0.96
A7	21±0.69	16±0.81	0.54±0.01	97.93±1.21
A8	16±0.77	14±0.47	0.48±0.03	99.78±1.05
A9	12±0.81	9±0.52	0.41±0.01	97.23±0.85
Broad range	12-54	9-40	0.41-1.02	97.23 – 99.78

n=3

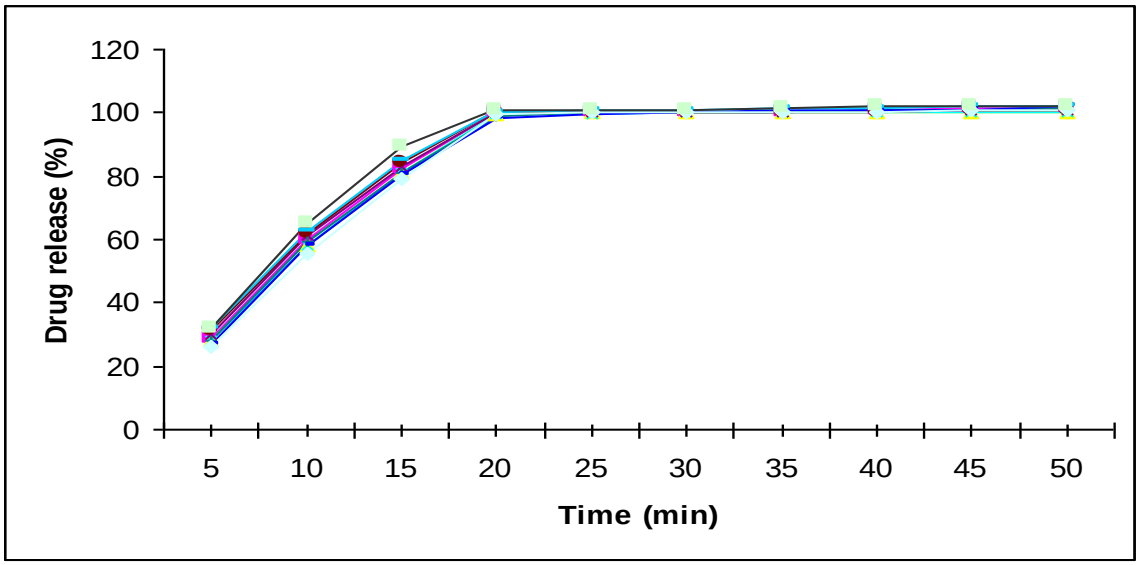

Fig. 3: Release profile of Candesartan Cilexetil from tablet formulations.

Table 6: Optimum formulation of mouth dissolving tablets of Candesartan Cilexetil.

Ingredient	Quantity (mg)
DRC (eq. to 50mg of Candesartan Cilexetil)	103.9
Crospovidone	22.5
Micro Crystalline Cellulose	20
Citric acid	10.5
Sodium saccharin	2.5
Menthol	1.5
Orange flavor	2.5
Aerosil	3.75
Mannitol	q.s.
Total	250

CONCLUSION

From the above experimental findings it can be concluded that:

- Fast dissolving tablets prepared by the Crospovidone are promising for rapid release of Candesartan Cilexetil.
- Tulsion 335 was selected for taste masking of Tramadol HCl.
- From this study it is possible to design suitable fast dissolving tablets containing Candesartan Cilexetil for the treatment of psychoses with more effectiveness and better patient compliance.
- Further in-vivo investigations are required to correlate in-vitro drug release studies for the development of suitable rapid release system for Candesartan Cilexetil.

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CONFLICTS OF INTEREST

The author declared no conflicts of interest.

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