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Research Article

DESIGN AND DEVELOPMENT OF RAPID RELEASE MOUTH DISINTEGRATING TERBUTALINE SULPHATE TABLETS-A COMPARATIVE EVALUATION OF SUPERDISINTEGRANTS AND THEIR COMBINATIONS

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ABSTRACT

The concept of formulating mouth disintegrating tablets containing terbutalinesulphate offers a suitable approach in serving desired objective of rapid dissolution with increased bioavailability to provide quick relief in episodes of asthmatic conditions. Development of such fast disintegrating dosage forms will assist in solving the problems encountered in administration of drugs having difficulty in swallowing without need of water, hence improving patient compliance. Prototype tablet formulation containing superdisintegrants like kyron T-314, indion 414, tulsion 339, crospovidone and their combinations were formulated by direct compression technique. Tablets were evaluated for appearance, weight variation, hardness, friability, content uniformity, wetting time, *in vivo* disintegration time and mouth feel, *in vitro* disintegration test, *in vitro* dissolution studies and stability studies. Comparison studies were done on the best devised formulation with conventional marketed product. Tablets were physically sound with respect to their quality parameters. Developed formulation was found to be innovative approach exhibiting faster rate of drug release to possess quick relief from asthma.

Keywords: Terbutalinesulphate,mouth disintegrating tablet, kyron T-314, indion 414.

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by hyper responsiveness of trachea bronchial smooth muscle to variety of stimuliresulting in narrowing of air tubes, increased secretions, and mucosal edema leading toobstruction of air pathways causing difficulty in breathing, wheezing cough and chest congestion. The treatment of asthmatic symptoms with conventional solid oral dosage forms are often associated with a slower onset of action, and inconvenience for pediatric, geriatric, bedridden, nauseous or non compliant patients. Oral liquids require careful handling. Aerosol systems fail to deliver the actual dose and are less potable, while dry powder inhalers cause clogging of device and require skillful operation. A mouth disintegrating tablet form which disintegrates rapidly in saliva without the aid of water would thus be a perfect alternative[1]. A Mouth Disintegrating tablet (MDT's)are uncoated tablet;when placed in mouth, disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva and can be swallowed in the form of a liquid[2].

Terbutalinesulphate is an orally active selective β_2 adrenergic agonist. There is a need to provide faster onset of action to immediately relieve acute asthmatic attack[3]. Objective of the

present study was to develop novel drug delivery system by simple direct compression technique. Terbutalinesulphate rapid release mouth disintegrating tablet were designed to provide drug in a more accessible form for quick relief of asthma thus increasing drug bioavailability by offering a potential mucosal absorption and avoiding first pass metabolism. The basic approach used in development of Mouth Disintegrating tablet is use of superdisintegrants which provides instantaneous disintegration of tablet after placing on tongue, thereby releasing the drug in saliva.Additionally, providing increased absorption potential through the buccal and esophageal mucosa as saliva passes into stomach. It also aims at overcoming the difficulty in swallowing and hence improving patient compliance.Also, this dosage form offers an advantage of convenience of administration while travelling where there may not be an access to water[4].

MATERIALS AND METHODS

MATERIALS

The materials used include terbutalinesulphate (gift sample from Blue Cross Laboratories, Verna-Goa), kyron T-314 (gift sample from Corel PharmaChem, Ahmedabad), indion 414 (gift sample from Ion exchange (India) ltd, Mumbai), mannitol& aspartame (gift sample from Glenmark Pharmaceuticals, Colvale-Goa). Microcrystalline cellulose (Avicel pH 102) was gift sample from Geno Pharmaceuticals, Tivim-Goa. Crospovidone, aerosil, orange encapsulated powder and american mint DC were gift sample from Wallace Pharmaceuticals, Ponda-Goa. All the other chemicals used of analytical grade were procured from LobaChemePvt Ltd Mumbai.

METHODS

Preformulationstudies

Identification of drug was carried out by FTIR (JASCO 4100). Standardization of the drug was carried out using UV spectrophotometry [Lambda 25 UV/VIS Spectrometer (Perkin Elmer)]. IR spectral analysis of the formulations was performed to assess drug excipient compatibility. Preliminary studies were carried out on the tablets using different concentrations of superdisintegrants. Thus, after evaluation of the quality parameters and subjecting to *in vitro* disintegration and *in vitro* dissolution studies the final concentrations of the superdisintegrants were optimized. Based on this preformulation data, the optimized formulations for further investigation were decided.

Formulation

Mouth disintegrating tablets each containing 5 mg of terbutalinesulphatewere prepared using superdisintegrantskyron T-314 (KYR T- 314), indion 414 (IND 414), tulsion 339 (TUL 339), crospovidone (CP) and their combinations by direct compression technique (Table 1).Good palatability was obtained by adding flavors and using citric acid along with aspartame and mannitol. The average weight of the tablet was 100 mg.The ingredients were sifted through a 40# mesh and then the required quantities were weighed. All the ingredients except the lubricant and the flavoring agents were uniformly blended. After mixing the drug and the excipients for further 20 min, flavoring agent was added and further mixed for additional 2 minutes. The tablet mixture was then compressed using Cadmach single station tablet punching press using 7mm standard concave punch. Formulated tablets of terbutalinesulphate are as shown in figure 1.

Evaluation of mouth disintegrating terbutalinesulphate tablets

The calibration curve was obtained by preparing aliquots of working standard solution of terbutalinesulphate in distilled water and the absorbance at 276 nm was measured after suitable dilution using Lambda 25 UV/VIS Spectrometer.

Visualexamination

Uncoated tablets were evaluated for physical appearance by visual assessment and uniformity of thickness using vernier calipers.

Weightvariationtest

Twenty tablets were selected randomly from each of the ten formulations, weighed individually and average weight was calculated[5].

Hardnesstest

Ten tablets were randomly picked from each of the ten formulations and the hardness expressed as kg/cm^{2}was determined using Monsanto Hardness Tester[5].

Friabilitytest[5]

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Initial weight) and transferred into the Friabilator. The

friabilator was operated at 25 rpm for 4 min. The tablets were then reweighed (Final weight).The percentage friability of tablets was calculated by

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

Contentuniformity

To find content uniformity of tablet, spectrophotometric method was followed. Previously weighed tablet was dissolved in 70 ml of distilled water in 100 ml volumetric flask and was shaken for 10 min. Final volume was made upto 100 ml with distilled water. The solution was then filtered and then dilution was made i.e 1 ml of solution was diluted to 25 ml. The absorbance of resulting solution was determined at λmax of 276 nm using suitable blank[6].

Wettingtime

This test mimics the action of saliva in contact with the tablet. Wetting time was measured by placing tablet on a piece of tissue paper folded twice in a small culture dish containing 10 ml buffer of pH 6.8. Time required for complete wetting was measured[7].

***In vivo* disintegration time and mouth feel**

The time (in sec) taken for complete disintegration of the tablet on the tongue was noted. It was determined by placing tablet on tongue and allowed to disintegrate without biting or drinking water[8].

***In vitro* disintegrationtest**

The *in vitro* disintegration time of a tablet was determined by dropping a tablet in a beaker containing 5 ml of pH 6.8 phosphate buffer maintained at 37±0.5°C. The beaker was shaken intermittently. Time (in sec) taken for complete disintegration of the tablet with no palpable mass remaining in the beaker was measured and recorded[8].

***In vitro* dissolutionstudies**

The dissolution studies on mouth disintegrating tablets were performed using USP II paddle apparatus. The tablets were introduced into the dissolution vessel containing 900 ml of distilled water, thermo stated at 37±0.5°C, and stirred at 50 rpm. 10 ml of the dissolution fluid was withdrawn after every 2 min, for a period of 30 min. The samples were filtered and analyzed using UV spectrophotometer at 276nm.

The drug release of the best devised formulation was compared with that of conventional marketed tablet of terbutalinesulphate for content uniformity and dissolution profile[8].

Stabilitystudies

Stability testing on best devised formulation was done at 40± 2°C / 75 ± 5% RH for period of one month. The quality parameters namely hardness, friability, wetting time, content uniformity and *in vitro* disintegration time were evaluated.

RESULTS AND DISCUSSION

Visualexamination

Visual assessment revealed that all the formulations were concave, circular in shape and white in colour.Tablet thickness was almost uniform in all the prepared tablets falling within 2.87±0.008 to 2.93±0.0l0mm (Table 2).

Weightvariationtest

None of the tablets deviated from average weight by more than ± 10 % (Table 2).

Hardnesstest

Hardness of the tablets was maintained in the range of 2.04±0.089to 2.46±0.055 kg/cm^2, as these tablets are rapidly dissolving(Table 2).

Friabilitytest

The percentage weight loss in the friability test was less than 1% in all the batches. The tablets were able to withstand the mechanical shocks of the friabilator. Thus it can be concluded that the tablets possess good mechanical strength(Table 2).

Contentuniformity

The uniformity of drug content was found to contain 4.848 mg to 5 mg of terbutaline sulphate. (Table 2).Drug content claim of terbutalinesulphate was 5mg.

Wettingtime

The wetting time in all the formulations was very fast and the time required for complete wetting was found to be between 3.50±0.075 to 11.08±0.104 sec (Table 3). This may be due to the ability of swelling and also the capacity of absorption of buffer. This parameter is related to disintegration time in

the oral cavity as tablet is placed motionless on the tongue; hence correlation between wetting time and disintegration time in the oral cavity can also be made. The wetting characteristics of tablet are as shown in figure 2.

***In vivo* disintegrationtimeandmouthfeel**

The results of *in vivo*disintegration time and mouth feel are as presented in Table 3.

***In vitro* disintegration test**

The four superdisintegrants reportedly exhibit a broad range of intrinsic swelling capacity(IND 414 >KYR T- 314 >CP >TUL 339) yet all four are very effective disintegrants.The results of *in vitro* disintegration time are presented in Table 3. Disintegration of formulated tablet is as shown in figure 3.

All the tablet formulations disintegrated rapidly *in vitro* within 10.24±0.065to 14.07±0.130 sec, showing excellent disintegration. However, formulation F9 containing IND 414 and CP in combination exhibited fastest disintegration time of 10.24±0.065sec. The tablets containing individual superdisintegrants showed *in vitro* disintegration in the order CP > KYR T- 314 > IND 414 > TUL 339. Nevertheless, all four proved to be very effective disintegrants.

The tablets containing CP alone and its combination with other superdisintegrants showed faster disintegration than tablets containing KRY T- 314, IND 414 and TUL 339 alone and their combinations. KYR T-314 and TUL 339 displayed good disintegration time in combination with CP. TUL 339 alone took the longest time for disintegration.

***In vitro* dissolution studies**

It was observed that the type of disintegrant influences the drug release. The formulation F5 containing KYR T- 314 and IND 414 exhibited the fastest release rate of 99.04 % in 5 min followed by formulations FI, F2, F8, F4, F7, F9, F10, F3 & F6 respectively. A significantly higher rate of drug release was observed for formulation F5 containing KYR T-314 and IND 414 in 5 min, with a release of 99.04% followed by formulation F3 containing TUL 339 releasing 99.02 % in 12 min. Drug release from formulation F4 containing CP was 98.42% within 8 min. Formulations F10 containing KYR T- 314 with CP and F6 containing IND 414 and TUL 339 showed a drug release of 97.50 % and 97.86 % within 10 min and 14 minrespectively. At the end of 6 min, formulations F1, F2 and F8 showed a drug release of 96.24 %, 96.88% and 95.64% respectively. Formulation F9 and F7 showed a release of 96.80% and 95.60% in 10 min and 8 min respectively. Further comparisons between individual superdisintegrants showed the drug release in the order TUL 339>CP>IND 414>KYR T- 314 in 12, 8, 6and 6minutes respectively. Formulation F5 containing KYR T- 314 and IND 414 was chosen as the best devised formulation as it exhibited the highest rate of drug release and a fast disintegration. The results of *in vitro* release profile ofterbutalinesulphate tablets are as indicated in table 4 and graphically shown in figure 4, 5, 6 and 7.

Comparison with conventional marketed product

Drug content uniformity was found to be 4.925 mg. The marketed product gave 98.44% of drug release in 20 min. The comparison of *in vitro* dissolution profile of conventional marketed product and formulation F5, recorded in table 5 and depicted graphically in figure 8 showed that the formulation F5 with 99.04 % of drug release in 5 min has faster drug release in comparison with the marketed product. Terbutalinesulphaterelease was significantly faster from all the devised formulations as compared to the marketed conventional tablet formulation.

Stability studies

Not much variation or changes were observed in the formulation. The results are tabulated in table 6.

CONCLUSION

A stable, effective and pleasant rapid release mouth disintegrating tablet, with an excellent disintegration time and dissolution profile, was formulated using combination of kyron T-314 and indion 414 as superdisintegrants. The formulation was developed with desired objective to provide rapid dissolution characteristics and in turn increased bioavailability for quick relief in episodes of asthmaticattack. The technology fulfills the need for an economic, industry feasible method for these tablets involving conventional equipments. Undoubtedly, all the formulations showed

disintegration time, apart from fulfilling all compendia and other standard specifications, with much higher drug release rates.

ACKNOWLEDGEMENTS

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Table 1: Formulation of MDT's

Ingredients	Quantity (mg) present in each tablet									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Terbutalinesulphate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Kyron T-314	2.0	-	-	-	2.0	-	-	2.0	-	2.0
Indion 414	-	2.0	-	-	2.0	2.0	-	-	2.0	-
Tulsion 339	-	-	4.0	-	-	2.0	2.0	2.0	-	-
Crospovidone	-	-	-	4.0	-	-	2.0	-	2.0	2.0
Microcrystalline Cellulose	75.55	75.55	73.55	73.55	73.55	73.55	73.55	73.55	73.55	73.55
Mannitol	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Colloidal silicon dioxide	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Citric acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Orange encapsulated powder	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
American mint DC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Defined bulk weight per tablet was 100 mg containing 5 mg terbutalinesulphate.
F1 to F10 represents various tablet formulations of terbutalinesulphate.

Table 2: Evaluation of tablet parameters

Formulation Code	Thickness* (mm) (Mean ±SD)	Weight Variation# (mg) (Mean ±SD)	Hardness* (Kg/cm^2) (Mean ±SD)	Friability* (%)	Content of terbutalinesulphate* (Mean ±SD)
F1	2.87±0.008	100.3±0.949	2.28±0.259	0.0997	4.925±1.08
F2	2.91±0.008	99.9±0.994	2.36±0.152	0.2002	4.848±0.41
F3	2.89±0.009	99.9±0.876	2.08±0.179	0.1001	4.963±0.84
F4	2.91±0.008	100.2±1.317	2.38±0.217	0.1996	5.000±0.01
F5	2.87±0.010	100.1±0.876	2.32±0.110	0.1998	4.963±3.02
F6	2.92±0.011	99.9±1.370	2.04±0.089	0.3003	4.925±1.89
F7	2.88±0.007	99.9±0.738	2.38±0.217	0.1001	4.888±0.84
F8	2.93±0.008	99.8±0.919	2.04±0.089	0.2004	4.888±0.43
F9	2.93±0.010	100.1±0.738	2.30±0.274	0.2997	4.925±0.85
F10	2.92±0.005	99.9±0.738	2.46±0.055	0.2002	5.000±0.03

F1 to F10 represents the various tablet formulations of terbutalinesulphate.
*Each value represents a mean of 10 determinations.#Each value represents a mean of 20 determinations.SD denotes Standard Deviation

Table 3: Evaluation of tablet parameters

Formulation Code	Wetting time (sec)* (Mean ±SD)	*In vivo* Disintegration time (sec)* (Mean ±SD)	*In vitro* Disintegration time (sec)* (Mean ±SD)	Mouth Feel
F1	11.08±0.104	17.08±0.093	12.41±0.378	+
F2	10.53±0.476	18.34±0.308	13.33±0.496	+
F3	9.14±0.150	19.03±0.059	14.07±0.130	+
F4	3.54±0.316	16.29±0.259	11.12±0.115	+
F5	4.43±0.446	18.37±0.186	12.28±0.271	+
F6	4.94±0.050	18.70±0.125	12.52±0.465	+
F7	3.50±0.075	15.03±0.055	10.74±0.070	+
F8	4.09±0.013	16.19±0.178	12.14±0.128	+
F9	4.81±0.101	16.29±0.246	10.24±0.065	+
F10	4.35±0.076	17.02±0.038	10.51±0.035	+

F1 to F10 represents the various tablet formulations of terbutalinesulphate.

*Each value represents a mean of 3 determinations.'+' palatable mouth feel. SD denotes Standard Deviation

Table 4:*In vitro* release profiles of MDT's

Time (min)	Cumulative percent drug released ± SD*									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
2	73.62±1.56	72.36±2.56	61.56±2.85	71.64±1.22	55.62±2.88	57.78±1.55	60.84±2.55	79.56±1.56	77.76±1.27	55.62±2.23
4	92.80±0.05	84.86±1.08	73.32±1.84	81.80±1.66	74.60±1.97	65.80±1.89	77.00±2.64	87.64±0.99	85.10±1.44	77.30±1.23
6	96.24±0.85	96.88±0.56	79.82±1.99	94.14±0.98	78.22±1.85	76.32±1.22	84.00±1.05	95.64±0.07	87.70±1.98	78.26±1.99
8	-	-	81.88±0.98	98.42±0.26	86.00±0.95	84.36±0.89	95.64±0.66	-	95.10±1.54	92.48±1.02
10	-	-	84.88±0.87	-	99.04±0.08	93.46±0.08	-	-	96.80±0.99	97.50±1.54
12	-	-	84.06±0.88	-	-	97.46±0.28	-	-	-	-
14	-.	-	99.02±0.13	-	-	97.86±0.99	-	-	-	-

F1 to F10 represents various tablet formulations of terbutalinesulphate.
*Each value represents a mean of 3 determinations.
SD denotes Standard Deviation

Table 5:*In vitro* release profiles of best devisedMDTand marketed product

Time (min)	Cumulative percent drug released± SD*	
	F5	Marketed product
1	55.62±	61.56±
2	74.60±	66.74±
3	78.22±	73.28±
4	86.00±	78.56±
5	99.04±	80.42±
6	---	81.88±
8	---	84.06±
10	---	85.52±
12	---	87.70±
14	---	90.96±
16	---	94.24±
18	---	96.26±
20	---	98.44±

*Each value represents a mean of 3 determinations.
SD denotes Standard Deviation

Table 6: Stability studies

Formulation	Hardness (Kg/cm^2) (Mean ±SD)	Friability (%)	Content of terbutalinesulphate(mg) (Mean ±SD)	Wetting time (sec) (Mean ±SD)	*In vitro* disintegration time(sec) (Mean ±SD)
F5	2.32±0.110	0.1998	4.963±0.05	4.56±0.286	12.33±0.064

*Each value represents a mean of 3 determinations.
SD denotes Standard Deviation

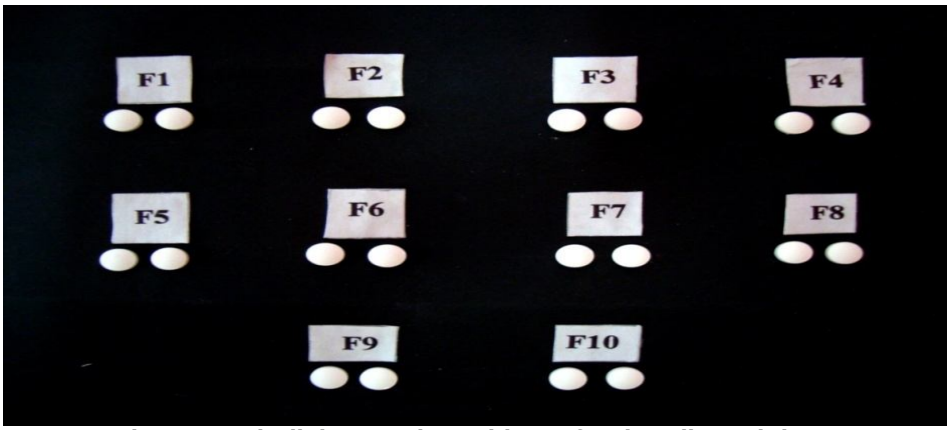

Fig.1: Mouth disintegrating tablets of terbutalinesulphate

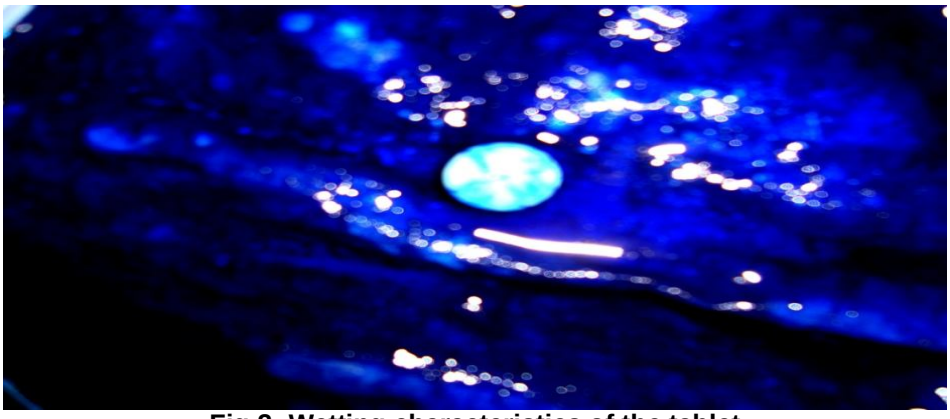

Fig.2: Wetting characteristics of the tablet

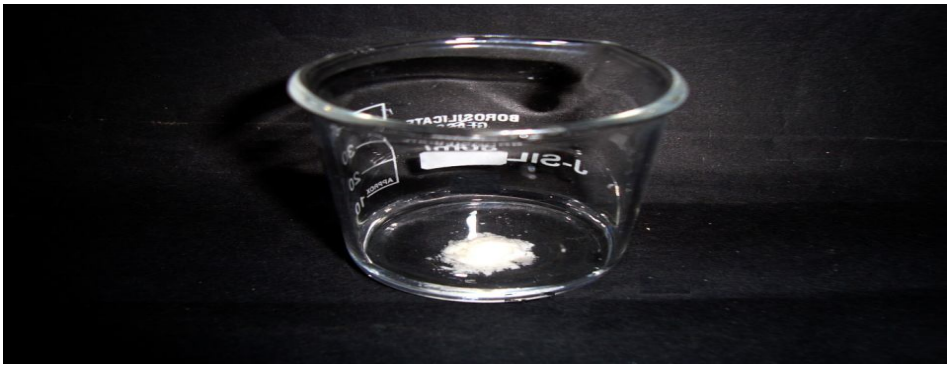

Fig.3: Tablet disintegration

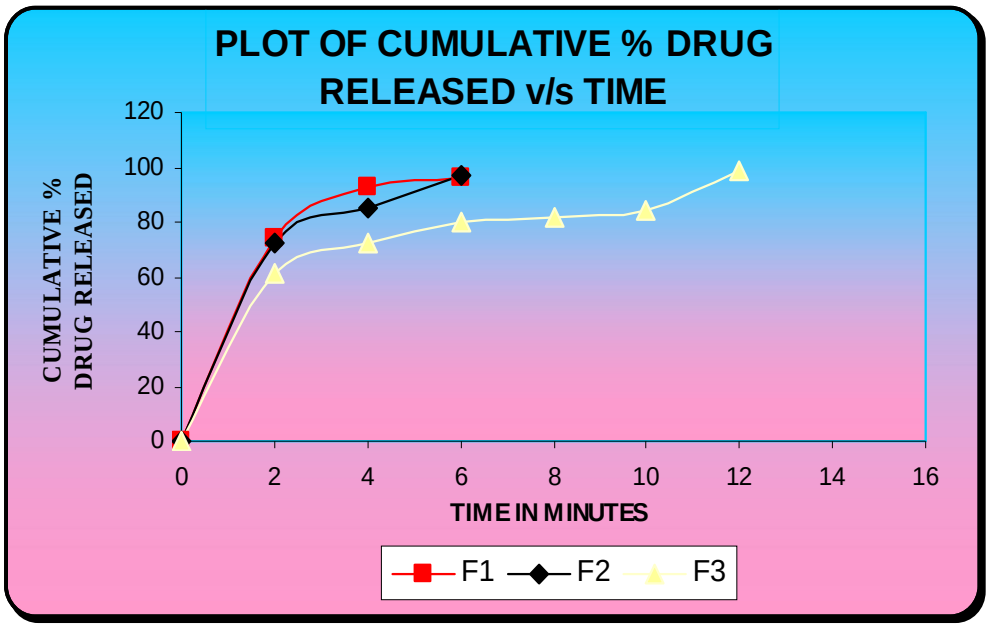

Fig. 4:Zero order plot of F1, F2 and F3

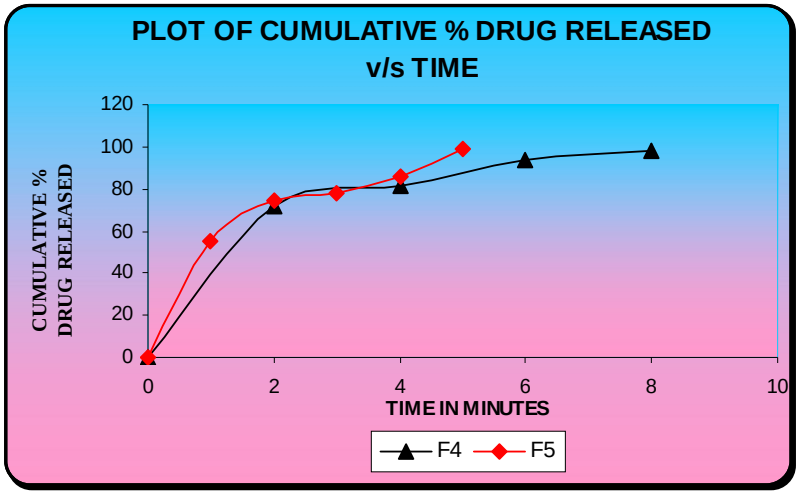

Fig. 5: Zero order plot of F4 and F5

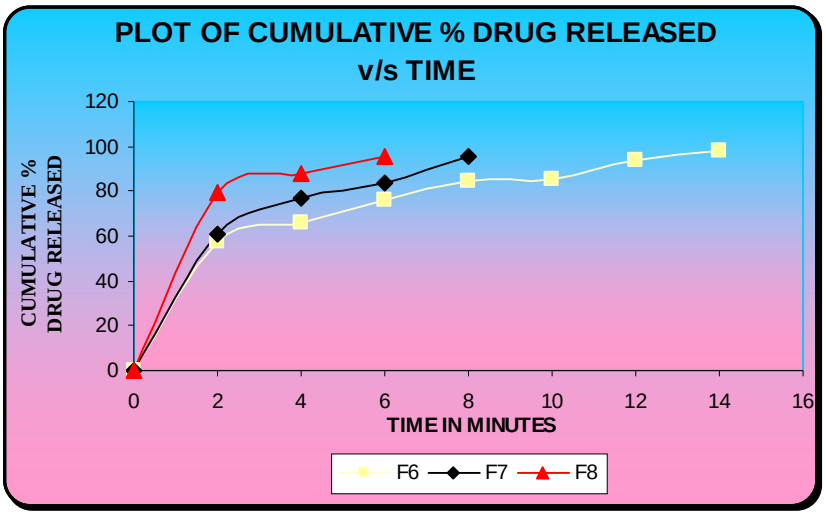

Fig. 6: Zero order plot of F6, F7and F8

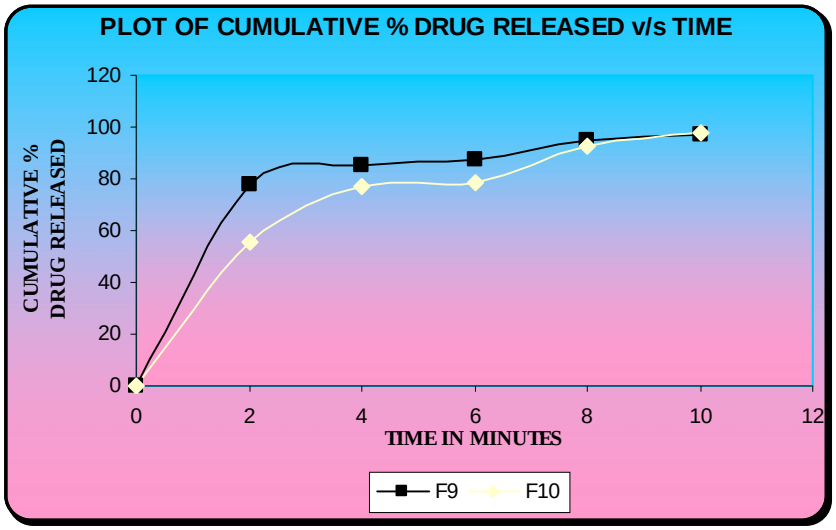

Fig.7: Zero order plot of F9 and F10

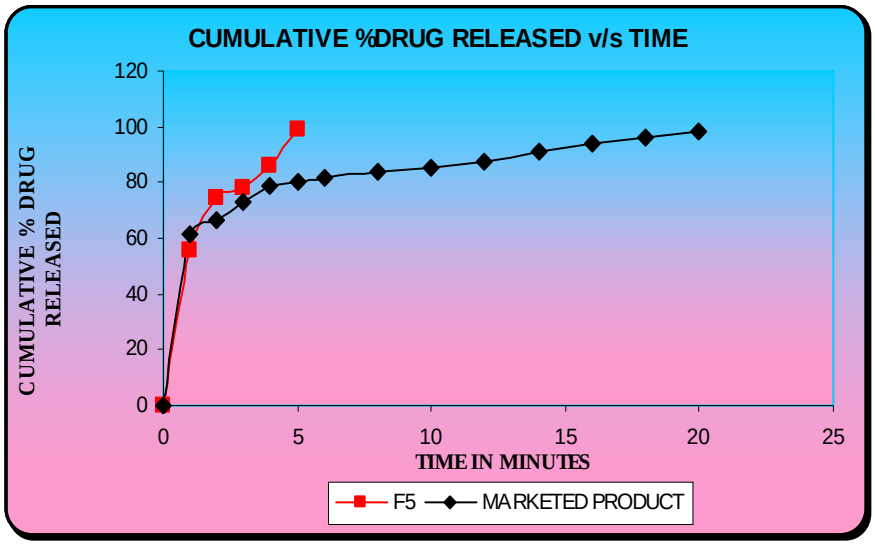

Fig.8: Comparison of the in vitro drug release profile of formulation F5 and marketed product

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