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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF PHENYLEPHRINE HYDROCHLORIDE

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ABSTRACT

Pharmaceutical invention and research are increasingly focusing on fast dissolving delivery systems which enhance desirable objective while minimising side effects. Nasal decongestant drugs like Phenylephrine hydrochloride have the oral problems like difficulty in swallowing, less oral bioavailability, first pass metabolism in conventional tablet dosage forms. The main objective of the formulation was to overcome such problems the decongestant drugs can be formulated in the form of fast dissolving tablets where the drug is rapidly disintegrated in mouth within fraction of seconds and improves the oral drug bioavailability. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient, almost economical method of drug delivery having the highest patient compliance. The formulated fast dissolving tablets were evaluated for drug content, thickness, in-vitro release studies and IR spectral analysis. In IR study reveals that more in no major shifting as well as non less of functional groups peak between the drug, polymer. In-vitro release profiles of 6 to 9 hours studies were found to have minimum or no drug release and at the end of 5 hours immediate release was observed. The in-vitro release study showed that the formulation F3 gives the better sustained effect over 99 % of drug was released at 5 hours. This study conclude that the polymers like crosspovidone, crosscarmellose and sodium starch glycolate are suitable for the preparation of fast dissolving tablets of phenylephrine hydrochloride and has immediate action in treatment of nasal decongestant.

Key words: *Phenylephrine hydrochloride, Super-disintegrants, Bioavailability.*

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INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery irrespective of its physical form (solid, semisolid, or liquid dosage form) , involves varying extents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal tract. Pharmaceutical products designed for oral delivery that is currently available on prescription and over-the-counter markets are mostly the immediate-release type, which are designed for immediate release of drug for rapid absorption. Because of their clinical advantages over immediate-release pharmaceutical products containing the same drugs. A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dissolving tablet or oral dispersing dosage form. The concept of Fast dissolving drug delivery system (FDDS) emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules.[1]

Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablet may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of FDTs. Bioavailability of a drug depends on absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of drug mainly depends on physical and chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet. The drug will dissolve at a slower rate from a non-disintegrating tablet due to exposure of limited surface area of the fluid. When we put FDTs on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus 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[.2] United States Food and Drug Administration defined ODTs as “A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue.” The disintegration time for ODTs generally ranges from several seconds to about a min.

Significance:[3]FDTs offer all the advantages of solid dosage form and liquid dosage form along with special advantage which include:Improved patient compliance, rapid disintegration of tablet result in quick dissolution and rapid absorption which provide rapid onset of action. Useful for pediatric, geriatric and psychiatric patientshaving difficulty in swallowing tablet.

MATERIALS AND METHOD:

Materials:

Phenylephrine hydrochloride, crospovidone were obtained from Knox pharma Ltd, Solan, H.P, India. Croscarmellose, sodium starch glycolate were gifted from Alembic Pvt. Ltd, Vadodara, India. Magnesium stearate, Lactose Monohydrate and Sodium Lauryl Sulphate (SLS) were gifted from S.D. Fine chem. Ltd, Mumbai, India. All the other chemicals and reagents were either analytical or pharmaceutical grades.

Preformulation Study: Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when

combined with excipients. It gives extensive information to bring out good quality at high standard at which optimal dosage desired. Preformulation studies were performed on the drug (API), which included melting point determination, solubility and compatibility studies.

Bulk density, tapped density, Hausner's ratio, carr's index and angle of repose was performed for polymeric blends.

Determination of solubility:[4]The solubility studies of phenylephrine hydrochloride were done by solubilising the drug in various preferred solvents with incremental amounts by a factor of 10. This test was carried on until the drug was fully solubilised in the respective solvent and shows no signs of cloudiness or precipitation.The preferred solvents for the solubility study of Phenylephrine hydrochloride are methanol, chloroform, acetone, water.

Determination of Melting Point:[5] Melting point of drug sample was performed by using Thiele's tube method. A fine powder of phenylephrine hydrochloride was filled in a capillary tube, previously sealed at one end and the capillary tube was tied to the bottom of the thermometer. The thermometer and capillary tube were immersed in to the liquid paraffin taken in the tube. Bottom of the tube was heated gently by means of burner. When the sample starts to melt the reading was recorded.

Determination Of λ_{max} :[6] Phenylephrine hydrochloride (10 mg) was weighed accurately and transferred in 10 ml of volumetric flask. It was dissolved in methanol and filtered it. Then filtered solution was diluted up to 100 ml with phosphate buffer (pH 6.8). The solution contained 1000 µg of phenylephrine hydrochloride per ml of the solution. The solution (1ml) was diluted further to 100 ml with the same solvent. The final solution contained 10 µg of phenylephrine hydrochloride per ml of the solution. Standard solution (10 µg/ml) was scanned in spectrum mode against a solvent (phosphate buffer pH 6.8) as blank between the range of 200-400 nm by using UV-visible spectroscopy to determine the λ_{max} (wavelength of maximum absorbance) of the drug.

Development of Calibration Curve for phenylephrine hydrochloride tablets (λ_{max}): Phenylephrine hydrochloride (10 mg) was weighed accurately and transferred in 10 ml volumetric flask. It was dissolved in methanol and filtered it. Then the filtered solution was diluted up to 100 ml with phosphate buffer (pH 6.8) to obtain a stock solution of 1000 µg of phenylephrine hydrochloride per ml of the solution (Recognized as stock solution A). From this stock solution A, 1ml of solution was taken and diluted further to 10 ml with the same solvent to obtain a stock solution of 100 µg of phenylephrine hydrochloride per ml of the solution (Recognized as stock solution B). From this stock solution B, various aliquots (1,2,3,4,5 ml) were taken and diluted to 10 ml with phosphate buffer (pH 6.8) to give a final concentration of 10, 20, 30, 40, 50 µg/ml. Then the absorbance of these solutions was measured at 240 nm against phosphate buffer pH 6.8 as blank and the corresponding values were plotted as a calibration curve.

Drug-polymer compatibility studies: The Fourier-transformed infrared spectra of phenylephrine and mixture of phenylephrine hydrochloride with sodium starch glycolate were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400-4600 cm-1 and the resolution was 4 cm-1. It is shown in fig.1,2.

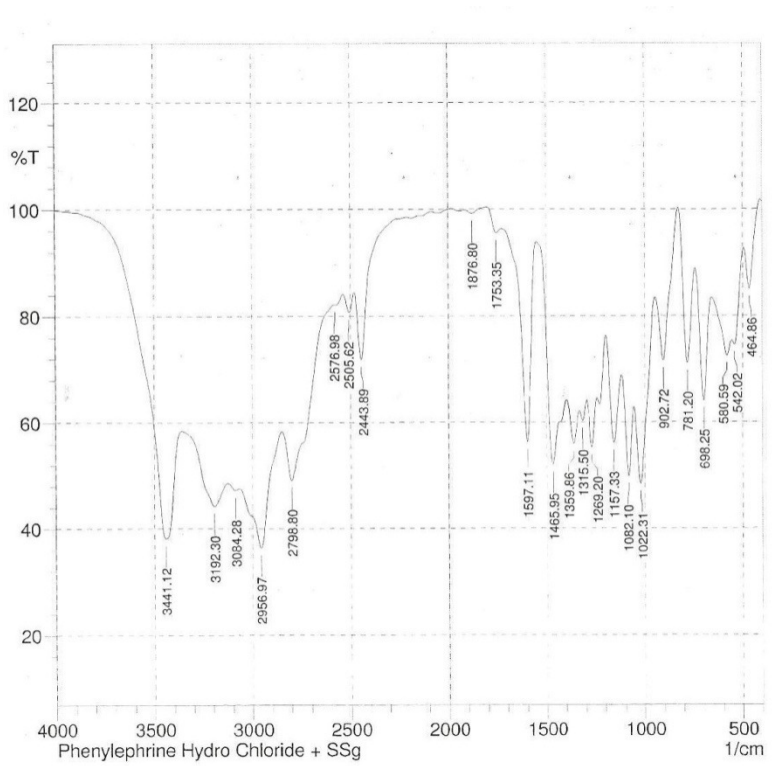

Fig 1. FTIR spectra of Physical mixture of Phenylephrine Hydrochloride

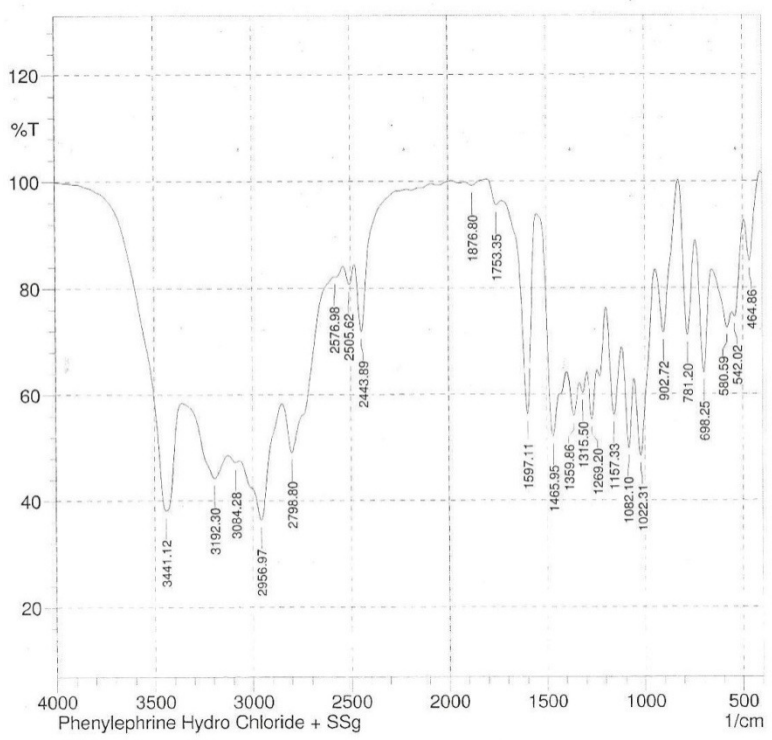

Fig 2. FTIR spectra of Phenylephrine

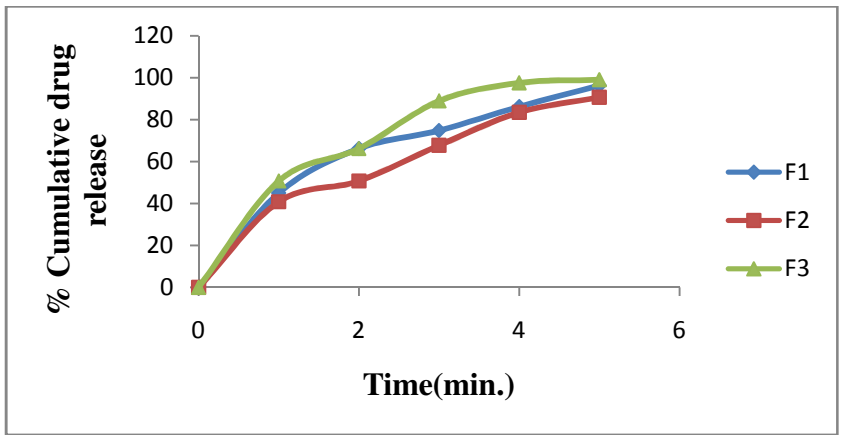

Fig 3: dissolution profile of F1 and F2 and F3

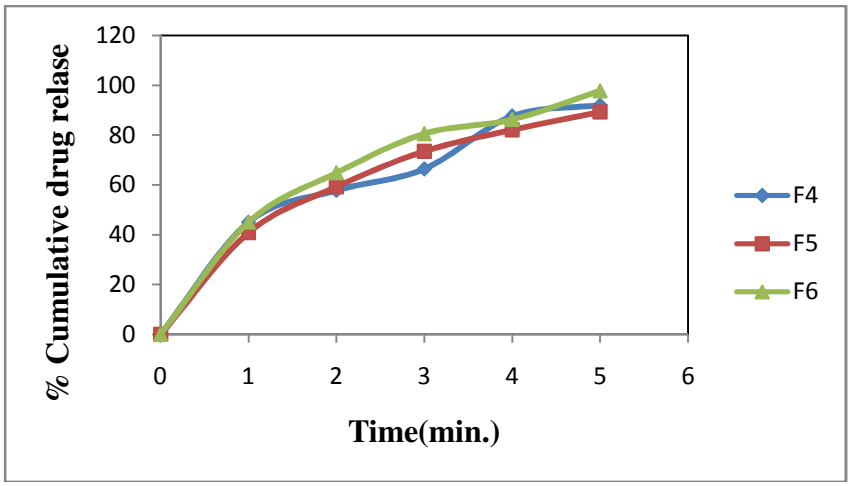

Fig 4: dissolution profile of F4, F5 and F6

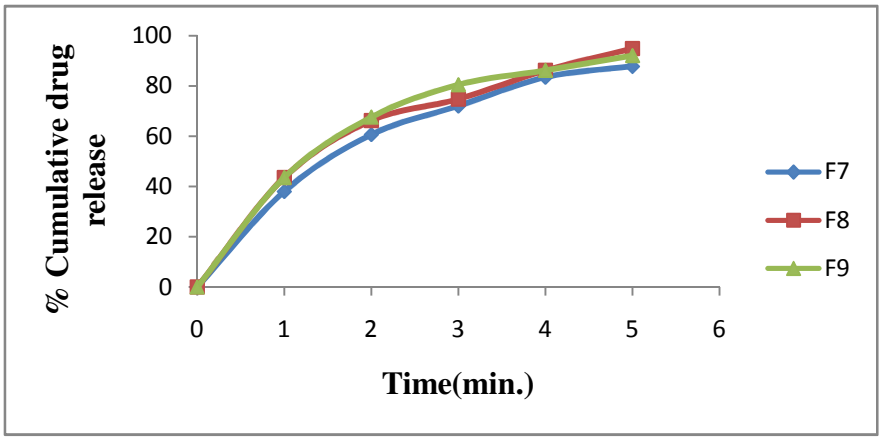

Fig 5: dissolution profile of F7, F8 and F9

Hydrochloride and Sodium Starch Glycolate

Formulation development: In this work, direct compression method with the aid of superdisintegrants was attempted for formulation development of fast dissolving tablets of phenylephrine hydrochloride. The phenylephrine hydrochloride tablets are available in 10mg-20mg doses in the market. Dose of 20 mg selected for the present study. Development of the formulation in the present study was mainly based on the type and concentration of polymers and the properties of the drug. Various polymers in different

concentrations (10.6%, 6.6% and 2.6%) were used so as to get tablets with good physical properties. The formulation design of fast dissolving tablets of phenylephrine hydrochloride is shown in Table 1.

Table No. 1: formulation of the tablet

Sr No	Ingredients	Quantity (mg)
1	Phenylephrine hydrochloride	20
2	Mannitol	91
3	Microcrystalline cellulose	27
4	Crospovidone	4
5	Aspartame	6
6	Magnesium stearate	1
7	Talc	1
Total weight		150 mg

Manufacture of phenylephrine hydrochloride fast dissolving Tablets:[7] Nine different formulations of phenylephrine hydrochloride fast dissolving tablets F1-F9 were prepared by using the ingredients as mentioned in the table. phenylephrine hydrochloride was used with Sodium Starch Glycolate, CP and CCS to formulate the fast dissolving tablets. All the ingredients were passed through #60 mesh separately, weighed and mixed in geometrical order. Then lubricant and glidant (# 200 mesh) were added and mixed for further 5 min. The blend thus obtained was directly compressed using 8 mm flat round punches into tablets of 150 mg on a 10-station rotary tablet machine (Clit, Ahmedabad, India).

Evaluation of tablets:[8]

Tablets were evaluated for weight variation, thickness, hardness, friability test, content uniformity test. These parameters are known as post compression parameters. These are shown in table no.2,3.

Table No 2: precompression parameters of the polymeric blend

Batch	Bulk density (w/v)	Tapped density (w/v)	Hausner's ratio	Carr's index	Angle of repose (θ)
F1	0.45	0.56	1.24	19.63	25.43
F3	0.44	0.54	1.28	18.51	26.25
F4	0.45	0.56	1.26	15.09	24.63
F5	0.43	0.53	1.23	23.21	25.36
F6	0.42	0.54	1.23	17.20	24.26
F7	0.45	0.54	1.27	16.45	23.36
F8	0.45	0.56	1.25	19.28	23.19
F9	0.46	0.53	1.24	16.76	25.43

Table No 3: Post compression parameters of tablets

Batch	%cumulative drug release in time 0,1,2,3,4,5 Hr	Thickness (mm)	Hardness (kg/cm^2)	Wt. variation	Friability (%)
F1	0,45.2,66.8, 44.8,86.2,96	3.216±0.020	5-6	149.45±0.811	0.431
F2	0,40.8,50.7, 67.7,87.4,90	3.207±0.011	5-6	151.01±0.910	0.418
F3	0,50.7,66.29, 88.9,97.5,99	3.383±0.024	5-6	150.02±0.741	0.538

F4	0,45.7,57.8, 66.4,87.66,92	3.304±0.013	5-6	150.44±0.540	0.472
F5	0,47.8,59.2, 73.4,82.3,89	3.258±0.017	5-6	148.89±0.487	0.446
F6	0,45.7,64.8, 80.5,86.2,97	3.247±0.019	5-6	150.01±0.519	0.516
F7	0,38.2,60.6, 72.2,83.4,87	3.238±0.031	5-6	150.60±0.818	0.596
F8	0,43.6,66.2, 74.8,86.2,94	3.252±0.027	5-6	149.55±0.973	0.576
F9	0,43.6,67.6 80.5,86.2,92	3.351±0.012	5-6	151.90±0.993	0.584

Thickness: Tablet thickness is measured by using a simple procedure. Five tablets were taken and their thickness was measured using Vernier callipers. The thickness was measured by placing tablet between two arms of the Vernier callipers (Mitutoyo).

Hardness Test: The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Friability: Ten tablets were weighed and placed in a Roche friabilator (Electrolab, India). Twenty pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then deducted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula.

Content uniformity:

For determining the content uniformity test, 10 tablets were taken and crushed, weight equivalent to 100 mg was taken and dissolved in SLS. Further dilutions were made to get the concentration of 10µg/ml. the solution was analyzed for Phenylephrine hydrochloride content by UV-Spectrophotometer at 345.5 nm by using SLS as a blank.

***In vitro* release study of tablets**

in vitro release studies of tablets were carried out in USP Type II (Paddle Type) apparatus by using 0.5% of SLS in water as a dissolution media. Rotated at 50 rpm and temperature maintained at 37 ± 0.5˚C. Sample was withdrawn periodically at the interval of 5 mins and analyzed by UV-spectrophotometer at 240 nm.

RESULTS AND DISCUSSION:

An absorption maximum was determined by scanning different concentration of solution of drug Penylephrine hydrochloride. It was found to be 240 nm and method obeys Beer's law in concentration range 2 to 10µg/ml, r^2 was found to be 0.0999.

Preformulation test of polymeric blends:

Bulk density, tapped density, Hausner's ratio carr's index and angle of repose was given in the Table 2. The angle of repose (θ) for all the formulation blends was below 30º indicating good flow property.

***In vitro* dissolution of tablet**: In vitro dissolution of the fast dissolvimg tablets was studied in USP XXIII type-II dissolution test apparatus (Electrolab, model: TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at $37^0 \pm 0.5^0$ C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 240 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of the drug released was calculated against time.

CONCLUSION:

The novel Fast dissolving drug delivery system for oral use was successfully developed and evaluated. The formulation consisted of a tablet containing a drug Phenylephrine hydrochloride. From the FT-IR study, the interference was verified and found that Phenylephrine hydrochloride did not interfere with the polymers used. The final optimized formulation was compared with marketed product of Phenylephrine hydrochloride tablets (Sudogest) which shows 91.34% drug release in 30 min. From this observation it was concluded that the formulated tablets of Phenylephrine hydrochloride were superior and effective in achieving patient compliance and also meeting all specifications of pre-compression and post compression parameters and stability studies.

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