INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.5 | Issue 3 | July- Sep -2016
Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of darunavir chewable tablets

[1]B. Padmasri*, [1]R.Kalyani*, [1]K.L. Deepthi, [1]V.Anil kumar, [2]D.Prasanth

[1]Department of Pharmaceutical Technology, Sri Venkateswara College of Pharmacy, Etcherla, Srikakulam, India.

[2]Department of Pharmacology, Sri Venkateswara College of Pharmacy, Etcherla, Srikakulam, India.

***Corresponding Author: B. Padmasri**
Email: padmasripharma@gmail.com

ABSTRACT

In the present work, chewable release tablets of Darunavir were prepared by the wet granulation method. All the tablets were subjected to weight variation, drug content uniformity, and hardness, and friability, dissolution, drug excipients interaction and short-term stability studies. Tablets prepared by the wet granulation method were found to be good without any chipping, capping and sticking. The hardness of the prepared tablets was found to be in the range of 4.2 to 6.4 kg/ cm2. The friability values were found to be in the range of 0.63 to 0.81%. Disintegration time was found to be in the range of 1-3min.Formulation F7 showed good results than rest of the 9 formulations in pre and post compression studies. The average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared. Formulation F7 (99.266) displayed maximum drug release within 1 hour and also showed good hardness and friability results. IR-spectroscopic studies indicated that there are no drug–excipients interactions. The optimized formulation follows first order kinetics.

Keywords: Darunavir, Wet granulation method and IR-Spectroscopic studies.

INTRODUCTION

Oral solid dosage forms

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules [1]. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products [2]. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reasons whenever a new chemical entity (NCE) has discovered [4, 19], which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by the oral route or not [2]. The oral route of administration still continues to be the most preferred route due to its manifold advantages including [5]:

Tablets and capsules represent unit dosage forms in which the accurate dose of the drug to show sufficient pharmacological action can be administered. In case of liquid oral dosage forms such as Syrups [6], Suspensions, Emulsions [7, 13], Solutions and Elixirs the patient is asked to administer the medication of 5-30 ml. Such dosage measurements are typically error by a factor ranging from 20-50 %, when the drug is self-administered by patient [8, 14].

Solid dosage forms are less expensive for shipping and less prone for the degradation when compared to liquid dosage forms [3].

AIM AND OBJECTIVE OF PRESENT WORK

Daurunavir has poor solubility in order to enhance its dissolution different alkalizers shall be used [9]. Tablets shall be evaluated for various parameters like, weight variation, content uniformity [10, 16], and in-vitro dissolution studies. Thus a significant increase in the drug dissolution rate in intestinal stimulated fluid (pH 7.4), slightly acidic (pH 1.2) and water is the intended objective of this work and to develop a robust and stable formulation of Daurunavir chewable solid oral dosage form and to optimize the process parameters [17, 18].

Tablets are single-dose preparations intended for oral administration. Administration of drugs through oral route is the most common and the easiest way to administer a drug. But it is a challenge in children who have not yet learned to swallow tablets. Hence chewable tablets are formulated to improve the compliance in children.

Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. These are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. Chewable tablets are designed for use by the children and such persons who may have difficulty in swallowing the tablets.

Additionally, chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action. A non-dissolving polymer matrix modified release dosage form containing the drug and other excipients that must be chewed but not swallowed to promote release of the drug from the dosage form in the oral cavity.

In the manufacture of chewable tablets, measures are taken to: ensure that the tablets are easily crushed by chewing; ensure that the tablets are palatable.

Chewable tablets are especially useful in the tablet formulations for children and are commonly employed in the preparation of multiple vitamin tablets. Wherever feasible and practical; the first step in the formulation of a chewable tablet is to obtain a complete profile of the active drug. This usually leads to the most efficient formulation of a stable and quality product as the drug usually dictates the choice of fillers, carriers, sweeteners, flavor compounds, and other product modifiers. Many of the excipients commonly used in tablet formulation are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chew ability. In general, these fall into the sugar category, although a combination of bland excipients with artificial sweeteners may provide a satisfactory alternative. Important aspects of chewable tablet manufacture are the proper incorporation of the coloring agent, assurance of necessary particle size distribution) maintenance of correct moisture content, and achievement of proper tablet hardness. All of these are the routine responsibility of the manufacturing department once the parameters have been established during development. Two common approaches are the use of low concentrations of light colors and the use of high-intensity mixing of reduced particle size materials in order to assure thorough blending. Mannitol is widely used as excipients in chewable tablets for its non-hygroscopic nature of moisture sensitive drugs. Chewable tablet formulation, particularly those containing pharmaceutically active agents, present issue of the organoleptic characteristics of odor, taste, appearance and mouth feel. The formula ingredients and manufacturing process both play a role in obtaining the desired organoleptic properties.

Advantages of Chewable Release

The advantages of chewable tablets include-

- palatability
- stability
- precise dosing
- portability

- Ease of delivery.

Disadvantages of Chewable Release Tablets

- Rapid drug therapy intervention is not possible.
- Sometimes may require more frequency of administration.
- Dose dumping may occur.
- Reduced potential for accurate dose adjustment.

METHODOLOGY

Table 1. Formulation darunavir chewable tablets

INGREDIENTS (mg)	FORMULATION CODE								
INTRA GRANULAR	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Darunavir	300	300	300	300	300	300	300	300	300
MCC PH 101	166.9	164.15	161.4	158.65	166.9	164.15	161.4	161.4	161.4
Mannitol	30	30	30	30	30	30	30	30	30
CP	2.75	4.125	5.5	6.875	-	-	-	-	-
CCS	-	-	-	-	2.75	4.125	5.5	5.5	5.5
Binder solution									
Pre gelatinized starch	24	24	24	24	24	24	24	12	19.2
Water	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
EXTRA GRANULAR									
MCC PH 102	20	20	20	20	20	20	20	20	20
CP	2.75	4.125	5.5	6.875	-	-	-	-	-
CCS	-	-	-	-	2.75	4.125	5.5	5.5	5.5
Mg.stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Aerosil	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Total weight(mg)	550	550	550	550	550	550	550	550	550

PROCEDURE INVOLVED

Step 1

Weigh the all ingredients in required quantity and then, pass through sieve no #40 and bend the mixture (drug, mcc, mannitol and SLS) in double cone blender for 15min [11].

Step 2

Preparation of binder solution:

Take the req. qty of PG starch and color in dissolve in purified water.

Step 3

Addition of binder solution to the above mixture and the wet mass was sieved through #40 is dried in an oven for 2 hours until the moisture is below 2%.

Step 4

Extra granular portion to the above dried granules was done by passing through #40 and the mixture was blended for 15min in double cone blender [12].

Step 5

Perform the flow properties of the granules.

Step 6

Tablets were compressed in round punches 9mm diameter. (Compression machine make: cadmach 16station roratory compression machine).

RESULTS AND DISCUSSIONS

Preformulation Study

Organoleptic Properties (Color, odor, taste and appearance)

Table 2. Results of identification tests of drug

S.NO	Parameter	Drug
1	Color	White to off White color
2	Odor	Odorless
3	Taste	Tasteless
4	Appearance	Crystalline powder

Melting point determination: Drug: Darunavir

Table 3: Results of Melting point determination test of drug

Reported Melting Point	Observed Melting Point
74 - 76	**76**

Determination of solubility

Soluble in methanol water and DMSO, dimethylsulfoxide, and N, N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

DRUG AND EXCIPIENT COMPATABILITY

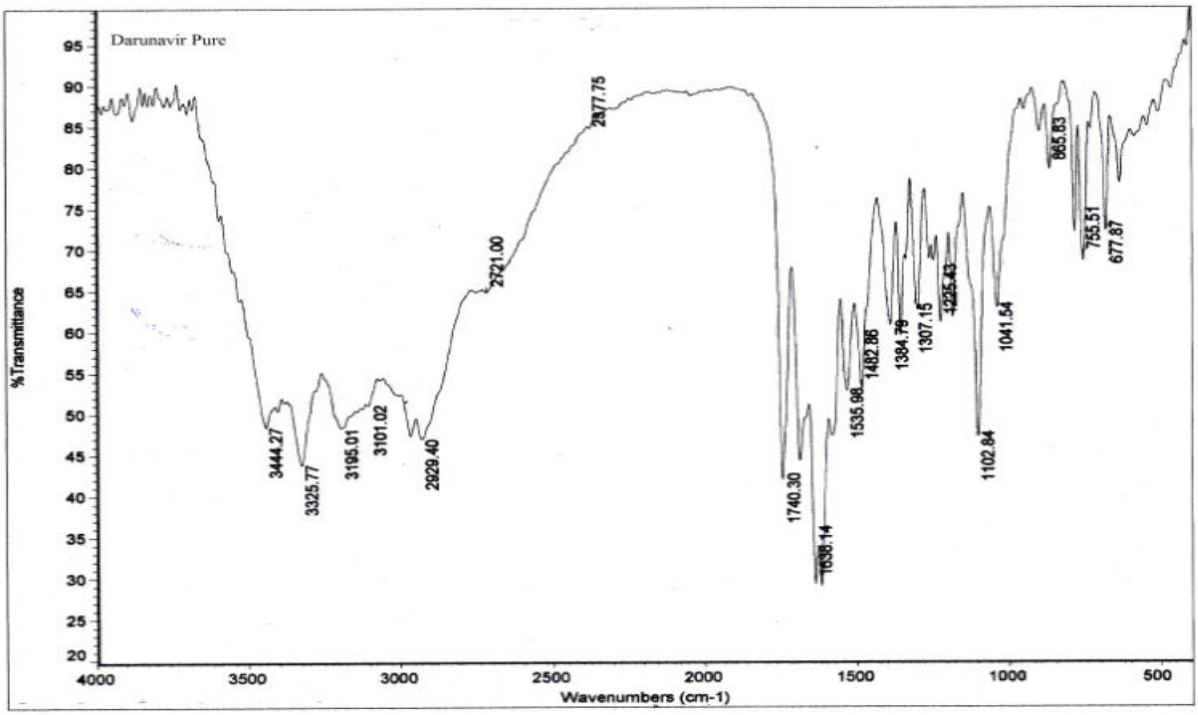

Fig no: 1 FTIR Spectrum of Darunavir pure drug

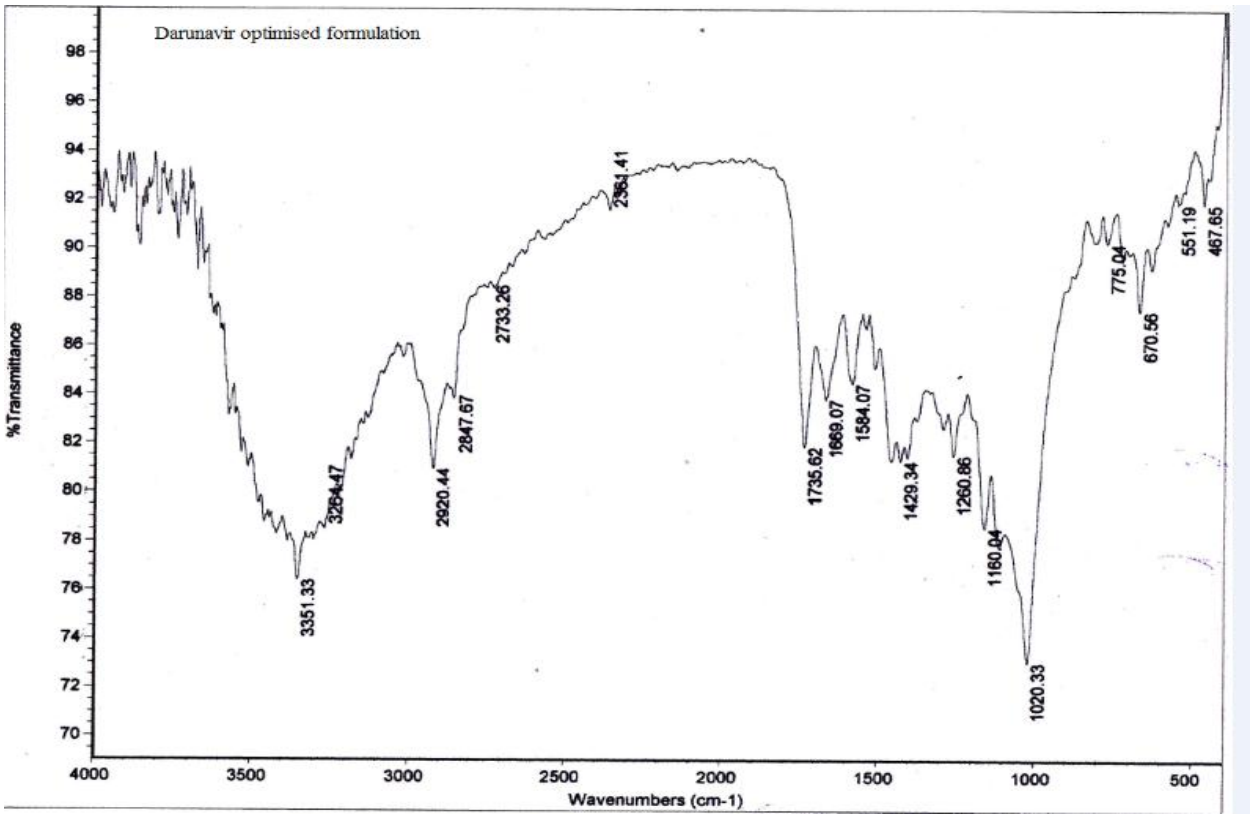

Fig no: 2 FTIR Spectrum of optimized formulation

UV-Spectroscopy - Analysis of drug

Ultraviolet Visible (UV-visible) spectroscopy

Drug sample showed wavelength of maximum absorption (λ-max) 220 nm.

Calibration curve of Darunavir in 0.1N HCl

Wavelength of maximum absorption: 220 nm.

Table no 4: standard curve of Darunavir pH 0.1N HCl at λmax 220nm

Concentration (µg/mL)	Absorbance
0	0
10	0.171
20	0.305
30	0.4460
40	0.620
50	0.752

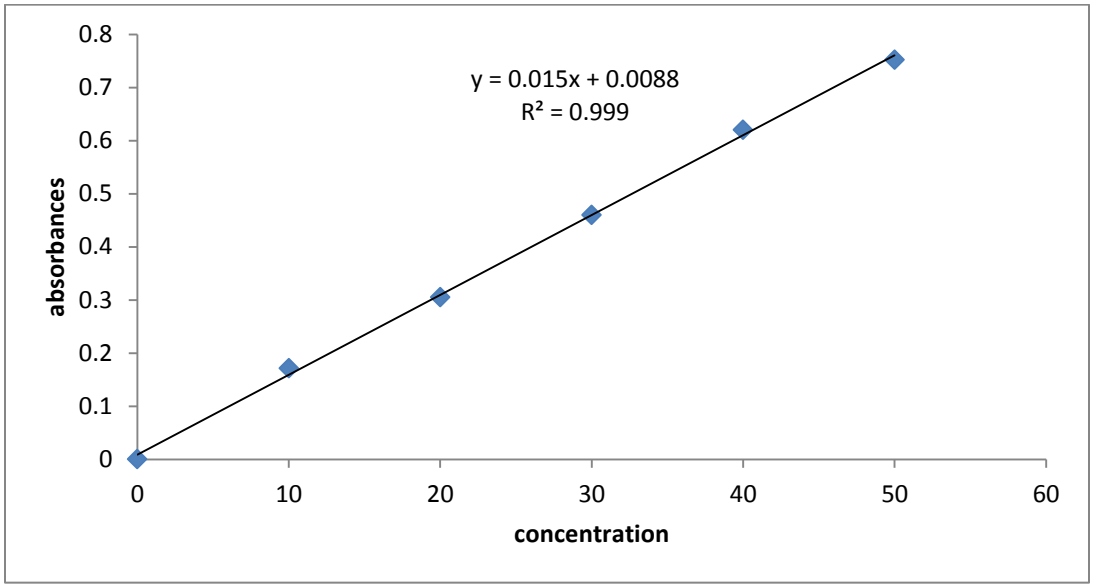

Fig No 3: standard curve of Darunavir in pH 0.1HCl buffer

Evaluation of Blend

Table 5. Bulk density, Tapped density, % Compressibility index, Hausner ratio and Angle of repose. (Precompression studies)

Formulation code	Bulk density * (g /ml)	Tapped density *(g/ml)	Hausner ratio*	Carr's index (%)*	Angle of *repose (θ)
F1	0.541±0.282	0.691±0.305	1.276±0.214	21.62±0.557	39.47±0.074
F2	0.484±0.394	0.615±0.353	1.27±0.516	21.30±0.648	38.73±0.094
F3	0.710±0.471	0.873±0.479	1.251±0.685	19.714±0.468	32.31±0.037

F4	0.712±0.165	0.870±0.620	1.206±0.473	17.126±0.376	32.44±0.062
F5	0.718±0.584	0.871±0.383	1.223±0.254	18.513±0.198	36.56±0.042
F6	0.410±0.285	0.483±0.413	1.178±0.274	15.113±0.421	34.44±0.053
F7	0.420±0.456	0.462±0.498	1.131±0.521	15.010±0.127	29.35±0.070
F8	0.541±0.552	0.691±0.736	1.276±0.441	21.62±0.453	38.41±0.124
F9	0.450±0.671	0.585±0.789	1.300±0.328	23.07±0.842	39.34±0.038

Evaluation of Tablets: Were given below in Table no.6

Table 6: Post compression studies

Formulation code	Weight variation *(%)	Hardness* (kg/cm2)	Friability (%)*	Thickness (mm)*	Drug content *(%)	Disintegration Time* (min)
F1	2.909±0.3494	6.4±0.102	0.72±0.334	2.6±0.02	99.28±0.1433	2±1.4748
F2	2.364±0.5855	6.3±0.241	0.68±0.440	2.6±0.05	97.16±0.1893	2.4±1.6665
F3	2.182±0.3356	5.8±0.433	0.69±0.681	2.7±0.06	96.1±0.0964	2.4±0.97896
F4	1.636±0.4466	5.9±0.465	0.64±0.463	2.56±0.04	98.5±0.06386	2.2±0.1355
F5	1.455±0.3578	5.6±0.769	0.66±0.438	2.75±0.05	97.68±0.1339	2.3±0.65637
F6	2.182±0.4677	5.7±0.654	0.68±0.656	2.6±0.03	99.41±0.08533	1.4±0.7870
F7	2±0.7686	5.9±0.466	0.65±0.7444	2.62±0.08	99.19±0.13	1.8±0.421
F8	2.364±0.6647	4.2±0.876	2.3±0.4794	2.6±0.04	94.6±0.1776	1.5±0.0579
F9	2.545±0.6464	4.5±0.436	1.80±0.3639	2.56±0.09	98.41±0.07846	1.9±0.0963

Physical characterization of IR Tablets of Darunavir

Tablet thickness, hardness, weight variation, friability and drug content of formulated Tablets of batches from F1 to F10 are presented in Table.

Uniformity of weight

All the prepared tablets of Darunavir were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±7.5%.

Hardness and friability

The hardness of the tablet formulations was found to be in the range of 4.2 to 6.4 kg/cm2. The friability values were found to be in the range of 0.63 to 0.81 %.

Uniformity of drug content

The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 97.16 to 102.6 percent (which was within the acceptable limits of ±5%.).

In -vitro drug release study

Paddle method Dissolution data of Matrix tablets formulations of Darunavir by Paddle method (USP II) are reported in Table7.

Table 7: Dissolution Values

Time in min	% Drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	36.883 ± 0.347	41.071±0.656	42.656 ± 0.2544	48.672 ± 0.3256	38.634± 0.3254	47.395 ± 0.3546	54.648± 0.0989	55.526± 0.0879	53.395 ± 0.2541
10	51.744 ± 0.466	52.04± 0.254	60.454 ± 0.5645	65.713 ± 0.3987	51.324± 0.2415	78.455 ± 0.6541	86.995± 0.3547	84.268± 0.3245	88.016 ± 0.2132
15	69.788 ± 0.467	76.846± 0.248	76.435 ± 0.6844	81.463 ± 0.5487	63.287±0.5412	87.748 ± 0.5412	93.247±1.245	92.052±0.6541	90.753 ± 0.2145
20	79.993 ± 0.678	83.128± 0.438	86.7813± 0.7454	85.7157± 0.5412	79.74±0.5216	90.248 ± 0.4123	98.152± 0.3245	96.692± 0.2145	95.457 ± 0.3214
30	80.647 ± 0.744	86.512± 0.568	90.413 ± 0.6547	92.7422± 0.2874	82.194± 0.2341	92.866 ± 0.5417	98.9673± 0.5463	97.222± 0.3214	97.698 ± 0.8241
45	84.188 ± 0.327	90.750± 0.659	93.110 ± 0.2468	96.346 ± 0.6854	85.781± 0.3214	93.258 ± 0.2149	99.0564± 0.2417	98.326± 0.3254	98.134 ± 0.6532
60	87.188 ± 0.338	93.855± 0.744	95.457 ± 0.543	96.674 ± 0.9874	89.973± 0.4123	94.857 ± 0.1487	99.266± 0.3481	98.524± 0.3241	99.087 ± 0.7452

In vitro dissolution study

In vitro dissolution studies were performed in 0.1N HCl on the above promising formulations. In the dissolution studies, the maximum drug release was found to be with formulation F7of maximum drug release (99.266%).

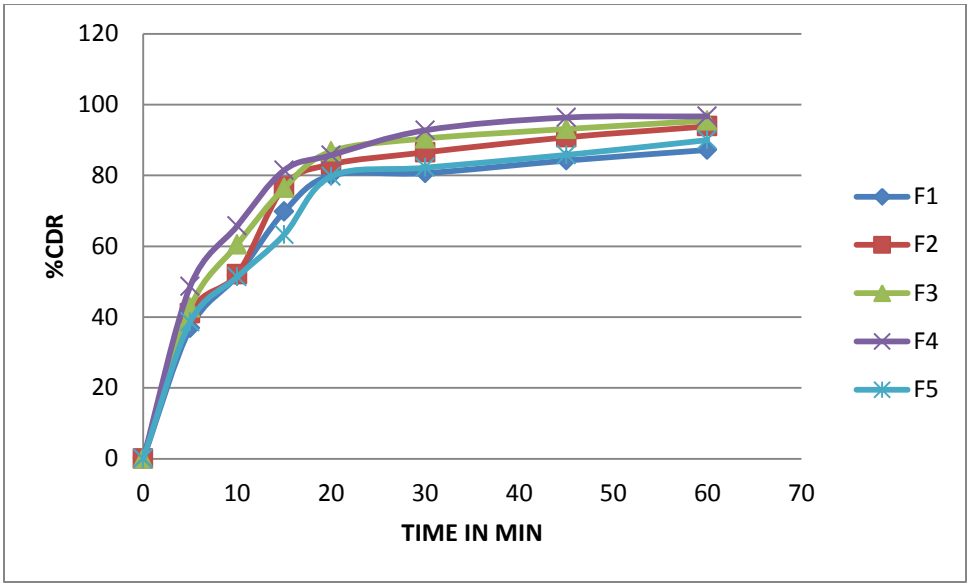

Figure 4.Cumulative % drug released for formulations F1-F5

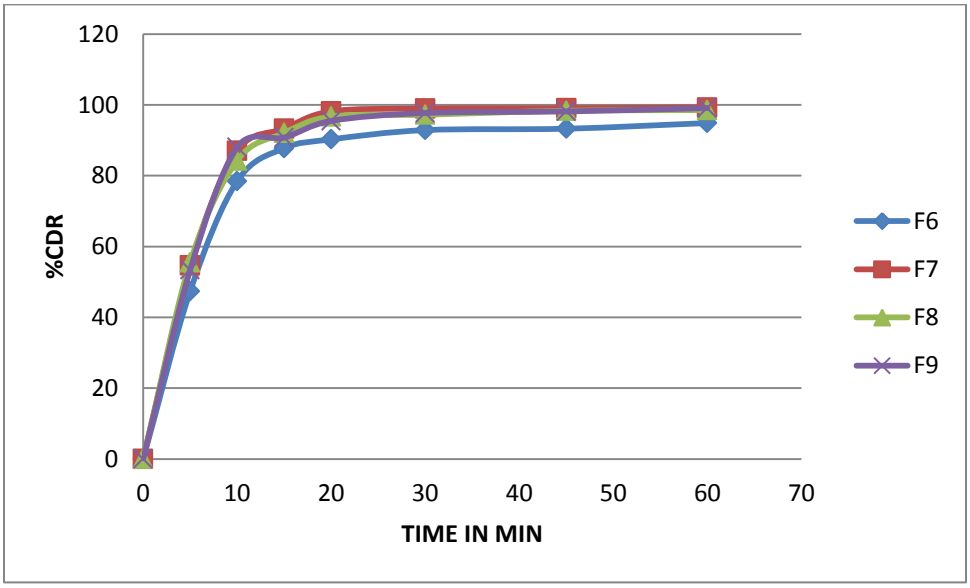

Figure 5. Cumulative percent drug released for formulations F6-F9

CONCLUSION

Basing on the results and discussion it was concluded that F7 formulation of Darunavir chewable tablets prepared by wet granulation method using 2% croscarmellose sodium showed better performance in all aspects of various evaluation tests. It had shown faster and maximum release within 1 hr. indicating faster onset of action and better bioavailability. Satisfying the objective of the study.

REFERENCES

[1]. Leon Lachmann , Herbert A , Liberman , Joseph L.Kaing , The theory and practice of Industrial Pharmacy; 293-303.

[2]. Aulton ME, Wells TI, Pharmaceutics, the Science of Dosage Form Design, *Churchill Livingstone*, Vingstone, London, 1988, 168.
[3]. *United States pharmacopoeia* (USP 29-NF 24), the official compendia of standards twin brook parkway, rockvillle. Asian Edition, 3, 27, 60-62, 2007, 2675, 2505.
[4]. *Indian Pharmacopoeia*, the controller of publication, Ministry of Health and Welfare. 1, 1996, 1178.
[5]. Subhramanyam CVS and Thimasetty J. Laboratory Manual of physical pharmaceutics. 5, 2005, 321-325.
[6]. Chavkin et al. United states patents, chewable molded tablets containing medicinally active substances, 5, 1998, 753, 255.
[7]. Kanig JL nad Rudinc EM, The mechanism of disintegrant action, pharm tech, Vienna,Austria, 2006, 50-63.
[8]. Kashid et al, United state patents, 2009/0269393, chewable Bilayer formulation, 2009.
[9]. Drug dosage form II (PHR312), advantages of chewable tablets, Lecture 6, pharos university, Alexandria, 2011.
[10]. Drug dosage form II (PHR312), advantages of chewable tablets, Lecture 7, pharos university, Alexandria, 2011.
[11]. Rippe E, Swarbrick J, Encyclopedia of Pharamaceutical Technology, Marcel Dekker Inc, Newyork, 3, 199, 149-166.
[12]. Mithal BM, A Text book of pharmaceutical formulation, Sixth edition, Vallabh Prakashan 1997.
[13]. Mohanachandran PS, Sindhumol PG, Kiran TS.Superdisintegrants: An Overview. *International Journal of Pharmaceutical Sciences* Review and Research. 6(1), 2011, 105-09.
[14]. Agarwal SP, Ragesh Khanna, Physical Pharmacy, New Delhi, CBS Publishers and distributors, 2, 2000, 247.
[15]. Harbir K. Processing technologies for pharmaceutical tablet: A Review. *International research Journal of Pharmacy*. *3(7), 2012, 20-23.*
[16]. Biradar, Formulation and Evaluation of chewable tablets. Int J Pharmacy and Pharm Sci. 2, 2006, 461.
[17]. Durga Devi NK, Rani AP, Madhavi BR and Mrudul BS, Int J Pharm Sci Bio 1(1), 2010, 20-24.
[18]. Lachman L, Lieberman HA and Kanig JL. The theory and practice of industrial pharmacy. 3, 1991, 293.
[19]. Roger walker, catewhittlesea, Clinical pharmacy and therapeutics, fourth edition, *Churchill Livingstone.*